PEDIATRIC CLINICS OF NORTH AMERICA

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Symposium on Pediatric Allergy

Lewis Webb Hill, M.D.
Harry L. Mueller, M.D.
Consulting Editors

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FORTHCOMING SYMPOSIA:

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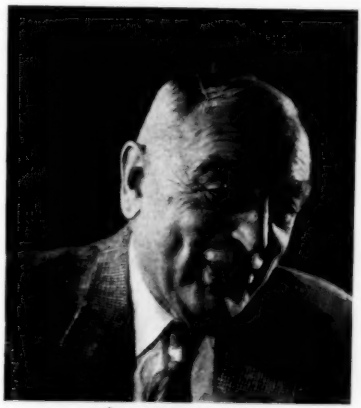
For

BÉLA SCHICK

Pioneer Allergist
Wise Physician
Kindly Gentleman



BÉLA SCHICK, M.D.

SYMPOSIUM ON PEDIATRIC ALLERGY

FOREWORD

LEWIS WEBB HILL, M.D.

HARRY L. MUELLER, M.D.

Consulting Editors

For some unknown reason many people become sensitized to things which encroach upon them, such as foods, animal danders, pollens and dusts; they are not able to withstand their environment. What does no harm to most people does do harm to them. This commonly happens before they have lived very long: hence the importance of allergy to pediatricians. *The world swarms with allergic children.*

Fifteen years ago there was no pediatrician who limited his practice to allergy, and there was no such thing as certification in pediatric allergy. Today there are 89 certified pediatric allergists in the United States and Canada. Most of them practice general pediatrics, with allergy as their special interest; probably about a dozen restrict their work to pediatric allergy.

Medical schools pay little attention to the teaching of allergy, and the average resident in most children's hospitals does not learn much about it, although there are special allergy clinics in many of them. When he starts practice, he is appalled to find that a high percentage of the children who come to him are allergic. If he feels that he knows too little to treat them properly, he sends them to a pediatric allergist if there is one nearby, or more likely to a general allergist.

Whether or not the general pediatrician treats these children himself depends to a large extent upon what he *wants* to do. He can learn

about allergy if he wants to. There are plenty of good books he can study, and he can go to the round tables and seminars provided by the American Academy of Pediatrics or to the short postgraduate courses given each year by the American College of Allergists and by the American Academy of Allergy. If he wants to develop this part of his practice, he can set aside a special office afternoon for allergic children, and as soon as this becomes known around town, he will have plenty of business.

It is certain to those of us who have written in this symposium that caring for allergic children is a worth-while way to spend the time, and that on the whole, ignorant though we be, we do reasonably well with many of them. We are, however, too often beset and vexed with discouragement: the asthmatic child who wheezes most of the time no matter what is done; the baby red as a lobster with intractable eczema who is in constant torment in spite of all our diets and salves; the older child with the thick, rhinoceros-like lichenified skin of chronic atopic dermatitis, who has acute exacerbations from all sorts of stimuli, immunologic and otherwise; the young child with hay fever who gags, strangles and coughs all night, in spite of many supposedly immunizing inoculations; the child with chronic unrelieved urticaria of entirely obscure causation—these are indeed discouraging children, and they are all too common.

The trouble is that they have a particular type of constitution. So little is known about the mechanism of the divergence from normality which governs this that it is not possible to change it and so to really *cure* them, any more than it is possible to change the color of their eyes or hair. Fortunately, most of them can be helped, some to a satisfactory degree. But there is room for great improvement in treatment; it is sure to come in time.

EMOTION AS AN "ALLERGEN"

LEO B. BURGIN, M.D.

"If you leave, I'll wheeze." Thus G.B., three and a half years old, threatened her mother. And indeed when her mother left, she wheezed.

Any physician caring for allergic children must at one time or another become aware of the effect of emotion on his patient's allergic difficulty, be it asthma or eczema. The sporadic attacks of asthma occurring on exposure to the cat or the dog or after a visit to the circus are readily explained as an allergen-antibody reaction in a sensitized person. Even the child with attacks associated with respiratory infection, i.e., asthmatic bronchitis, can be considered in the same category, although there may not be unanimity of opinion as to the specific allergen involved. However, the occurrence of frequent attacks of asthma without specific association with environmental factors, e.g., inhalants, ingestants, climatic changes, and so on, should raise the possibility that psychic factors may be playing a role. In some instances these may be obvious. In others only prolonged study can elicit the basis for the emotional difficulty.

It is important to note that before any allergen or emotion can produce a response characteristic of allergic disease, i.e., asthma, eczema, urticaria, the individual must be capable of reacting. This capacity to react is considered to be inherited; the individual is an "atopic" person. It is difficult to accept the concept that some patients suffering from allergic disorders do so on a purely psychogenic basis.[8]

In this paper "allergen" is meant to indicate that emotion may elicit a pulmonary or dermatitic response indistinguishable from that following exposure to true allergens.

ASTHMA

It has been observed that asthma occurs infrequently in mental institutions.[8] Leavitt, quoted by Funkenstein,[4] reports 0.08 per cent in a

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survey of 11,647 patients with functional psychoses. As the psychosis of an atopic person improves, asthma tends to return. The improvement of the asthma which occurs as the psychosis develops and the patient is hospitalized cannot be explained on the basis of hypoallergenic institutional environment. Some of the experimental aspects have been reviewed recently.[2]

CASE I. The opening paragraph of this paper is from the record of a female patient who entered this clinic at age 2 years and 10 months because of increasing frequency of attacks of asthma over the previous 7 months. Because of the association of her attacks with upper respiratory tract infections a tonsillectomy and adenoidectomy had been performed elsewhere without benefit. Inquiry brought to light the fact that a visit to an aunt who owned a dog would precipitate an attack of asthma in a matter of minutes of her arrival. Egg ingestion had produced vomiting, but not asthma.

By avoiding exposure to dogs in general the situation improved considerably over the next several months. It was observed that any attacks, minor or severe, had a definite effect on the mother. She would "go to pieces" when the child wheezed. Of great concern to this mother was the child's refusal to accept medicine from her. Yet when the father returned at night she willingly accepted the same medication without any special effort on his part. About this time G. began to threaten the mother with an attack under specific circumstances. If her mother planned to leave on an errand and the grandmother was the sitter, there was no trouble. If another person was engaged as a sitter, an attack followed the threat.

While arrangements were being made for psychiatric evaluation the mother was given active support by a physician. She was assured that though G. could produce an attack of asthma (wheezing) on demand, it could be brought under control. She was encouraged to "stand up to" the child. After several more visits the mother returned triumphant to the clinic one morning with the statement that she had "stood up" to G. When the latter had threatened an attack, the mother replied, "Don't you dare," and G. had not dared!

G. has continued to have difficulties. She refuses to absent herself from her aunt's house and the dog. Respiratory infections result in attacks. Although there have been fewer attacks due to emotional difficulties, these have not been completely resolved. Although allergic therapy is in progress (vaccine injections and attempts to limit exposure to dogs), she is being followed up by the psychiatrists.

Comment. In this case it is not unreasonable to assume that a number of allergens are responsible for her difficulty: (1) dog dander, (2) infection (bacterial sensitization?), (3) emotion. It is difficult to assess the relative importance of these allergens. Only by eliminating exposure to these allergens or raising tolerance by desensitization and psychotherapy can there be hope for success.

It is noteworthy that a reasonable beginning in resolving the emotional aspect was effected in the clinic by a willingness on the part of the attending physician to listen to the mother's story and to appreciate that emotional factors can influence allergic responses.

The following case illustrates the degree of success that is possible when emotional factors exist and attention is paid thereto.

CASE II. T.M. is now a high-school student of 17. After recurrent attacks of asthma starting at age 3 and increasing in frequency and severity he appeared in the clinic at age 8. According to his mother, he often was unable to walk to and from school because of the severity of his asthma. She frequently had to carry him up 3 flights of

stairs on return from school. He had already developed a barrel chest. Because of his almost total dependence on his mother and, to a less degree, on his father and because he did not respond to the usual symptomatic therapy, he was placed for temporary care in the "New England Home For Little Wanderers." He spent 6 weeks there while psychometric and psychologic evaluations were completed. Without change in therapy he became symptom-free almost immediately and continued so for the remainder of his sojourn (approximately 6 weeks).

It was observed that while in his own home he had been compliant and well behaved and expected to be "babied." His mother was overprotective and treated T. as a baby. Projective testing indicated that he was an aggressive child. At home the only way of expressing his aggressions (in an environment of goodness and indulgence) was the indirect one of controlling his environment through his illness. At The Home he had no need to inhibit his aggressiveness and consequently no need of his symptom, i.e., wheezing.

On return from The Home, T. was started on allergic therapy (pollen and house dust injections). Some of the emotional aspects of his difficulty were explained to the parents. During the next 3 months he seemed to improve. In August, coincident with the ragweed season, he seemed to have more difficulty.

Over the next 7 years allergic therapy and continued support to the family have resulted in considerable improvement. He has grown and developed quite well. Now in his senior year at high school, he has captained the football team and has done well enough to receive offers of football scholarships from several colleges in the East and South. At the moment he is 6 feet 2 inches tall and weighs 220 pounds.

Comment. It seems clear to me that the relatively quick improvement in this boy's difficulty after five years of incapacitating asthma was coincident with the clarification to the parents of the emotional factors involved. Continued anti-allergic therapy may have contributed to the over-all improvement. From an infantile dependent child of eight with severe asthma he has now emerged as an independent, mature young man with only minimal difficulty.

ECZEMA

The natural course of infantile eczema leads down one of 2 paths: remission at 18 to 24 months or continuation as the flexural eczema of childhood. In each instance other manifestations of allergy, e.g., asthma or hay fever, may make an appearance at a later date. This would appear to reinforce the concept that the initial eczema in each case was on an allergic basis. The reasons for these divergent courses remain unexplained. Over the years I have been impressed with the occurrence of permanent remissions by about 18 to 24 months in those instances in which the family has not only accepted the diagnosis as a fact, but also has followed through with the often difficult therapy as a challenge rather than an ordeal. On the other hand, when the infant is rejected and repulsed by the parents because he is a chore and unattractive, he may react by itching and scratching and exacerbate his eruption so that it continues into childhood. In several instances I feel I have been able to foretell what course the eczema would take on the basis of the concept expressed above. This is only a clinical impression not yet subjected to statistical analysis.

Although the course of eczema (flexural) in the older age group is also subject to remissions and exacerbation without reference to any special circumstance, there are situations in which it seems likely that emotions have played a part.

CASE III. E.A., now a young lady of 18, was first seen at the age of 2 with eczema involving the face and flexural areas. Over the next 10 years she attended the clinic perhaps not more than 2 or 3 times. The eczema remitted somewhat, though not completely, during the summer months. She had meanwhile had hay fever and pollen asthma. She was admitted to the wards at age 13 because of a severe exacerbation of her eczema. A program of pollen and house dust injections was begun.

After her discharge from the hospital the skin continued to show some activity. She was anxious and concerned that she would be unable to dress appropriately for her sister's wedding. To this end a short-term period of systemic steroids was planned. The skin cleared as was expected. The drug was stopped after 3 weeks. The skin now remained clear or nearly so, requiring only sporadic use of local steroid ointment for the next 2 to 4 months. Subsequently the skin remitted completely for the next 3 years. She meanwhile was receiving injections for hay fever. About 1 year ago (3 years after the short course of steroid therapy) there was a recurrence of the eczema. Judicious inquiry brought to light some difficulty with a "boy friend." When this was resolved, the skin again cleared and has remained so up to the present writing.

Comment. I am aware that eczema may remit and exacerbate at unpredictable times. In this case, however, it appears that the clearing of the eczema (by steroids) in time for the wedding relieved E. of anxiety to the extent that she remained free for almost three years. The exacerbation one year ago was easy to relate, at least in time, to an emotional circumstance. There were no other obvious causes: change of address, environment, diet, exposure to drugs, or the like. It would seem that concern about her appearance kept her agitated so that she itched and scratched. Under the effect of steroids the skin cleared and her anxiety disappeared. Later, when she was upset about her "boy friend," itching and scratching returned and the eczema exacerbated. Resolving the emotional difficulty acted like the removal of an offending inhalant or ingestant.

DISCUSSION

Many studies of the psychology of the allergic child have been made on those children who have had their disease a varying length of time.[1, 3, 7] These studies are retrospective in kind. It is reasonable to suppose that in most instances the difficulties—maternal rejection, hostility, and so on—occurred as a result of the disease rather than initiated it.

As part of a psychosomatic study of children with asthma, children sensitive to house dust by skin test, but who had continued to have difficulty despite injection therapy, were exposed to dust secured from their homes.[6] This was done by spraying their room (in the hospital) with this dust. No attacks of asthma were produced in 18 instances.

It is possible that had vital capacity determinations been made, some effect (decrease in vital capacity without audible wheezing) might have been noted. Yet these children, asthma-free in their house dust-filled room at the hospital, wheezed audibly again on return home. This raised the possibility of "emotional dust" as the responsible factor in these cases rather than house dust.

In our experience this "emotional-dust" sensitivity occurs only after the disease has existed for a number of months or even years. The child, frightened by his wheezing and respiratory distress, can be further disturbed by an apprehensive parent. This parental concern contributes to the child's concern and may result in insecurity in one instance and in another a source of power for the child over the parent or his social environment.

Thus an 11-year-old boy seen recently would have an attack of asthma whenever he was threatened with discipline. Another child has never taken a surprise examination at school. When he was thus confronted with an examination, asthma resulted and he was sent home. Even the severity of an attack may be determined by the child's emotional reaction thereto. A 12-year-old girl with chronic asthma gets along very well without medication, provided she is certain that there is medication available in the home. If, as has happened, an attack occurs and the mother has run short of medication, the attack becomes severe even though the child knows that medication can be secured shortly (personal communication from J. J. Cavanaugh, M.D.).

Since the emotional difficulties I have been considering do not occur until the disease has been present for some time, treatment should be prophylactic. To this end we have tried to inculcate parents when first seen with the concept of "intelligent neglect" of the allergic child. This implies a sympathetic but firm attitude towards the child and his problems. Discipline, when necessary, should be enforced. The threat by the child to induce an attack should be met coolly and casually by the parents. In this way emotion may be prevented from becoming a potent "allergen."

So far as possible allergic children should be permitted to do what their playmates do. The less these children are made to feel different, the less likely are they to become problems in behavior.

When psychogenic factors have existed for some time, it becomes necessary for the physician to support both patient and parent. This he can do, if he will, with each visit. The parents should be encouraged to discuss their problems. Guilt feelings, when present, should be dispelled. Direct criticism should be avoided. The child, too, should be encouraged to discuss his problems. Differences between child and parent can be resolved. In the presence of a severe behavior problem professional psychiatric help may be necessary. If good rapport has been

established with the parents, it then becomes a relatively simple matter to refer the patient to a psychiatrist. Yet, as with any chronic disease, the integration of all forms of therapy is imperative. The child's physician, be he pediatrician, family doctor or allergist, should assume the responsibility of this integration.

The following quotation from Lister[5] seems appropriate:

> Certainly, it seems that every physician must aim at attaining at least the status of an amateur psychiatrist. Almost every medical case has a psychosomatic aspect, and on inquiry it is found that the psyche has somehow been traumatized at work, at home or even at play so that the asthma, the ulcer or the dermatitis may fairly be regarded as the somatic expression of the injury sustained.

SUMMARY

Attention is called to the responses of some allergic children to emotional situations. These responses may be indistinguishable from that resulting from exposure to true allergens. Illustrative examples have been presented.

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EVALUATION OF THE WORTH OF SKIN TESTING

Mistakes and Fallacies

ARTHUR J. HORESH, M.D.

It is no longer considered acceptable practice merely to ascertain the presence of allergic disease. The well informed physician does not labor under the notion that children usually outgrow their allergies. The clinical pictures of allergic ailments are usually so characteristic that the diagnosis is rarely in doubt, even to the layman. Once the clinical diagnosis of an allergic condition is established, the physician proceeds to search for the cause. The diagnosis of allergic disease cannot be considered complete until the factor or factors responsible for the symptoms are discovered. This requires an allergic investigation, the purpose of which is to uncover the hidden excitant or excitants responsible for the patient's affliction. These eliciting agents are variable and specific for each case. The accepted measures of avoidance and reduction of allergenic exposures are in general more effective than any form of immunologic prophylaxis. The avoidance, when possible, of causal allergens usually has decisive significance in the management of severe or long-standing cases of allergic disease. In pediatric allergic disease, sensitivity is usually multiple. To prescribe effective treatment, all the factors which can produce the symptoms from which the patient suffers must be elucidated. The physician who does this is in a much better position to help his patients than the physician who treats these conditions only symptomatically. The successful management of allergic disease

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depends on recognizing the causative agents and eliminating them from the patient's environment. If this is impossible, he gives immunologic protection by means of specific hyposensitization.

The various methods of specific diagnosis are described elsewhere in this symposium and in any of the standard textbooks on allergy. There are also several articles on this subject[26, 31] from the pediatric point of view. The diagnostic methods include history, skin tests, mucous membrane tests, food diaries, elimination tests, environmental tests, exposure tests, and so forth. This clinic will describe one of the most important of these methods, allergic skin testing.

IMPORTANCE OF HISTORY

Although skin tests of various types play an important part in the specific diagnosis of allergic disease, it is important to recognize that they are only one part of the survey. All allergists generally agree that the history is the most valuable procedure available to unearth the incriminating factors.[33, 43] This part of the study is too frequently neglected through the desire to place all reliance on skin tests. The importance of a carefully taken and well interpreted history cannot be sufficiently emphasized. It gives more information for clinical guidance than any other single procedure. The physician dealing with allergic problems needs the cooperation and observations of an intelligent mother or nurse more than in any other clinical condition. Furthermore, the history must be a continuing matter,[35] extending over weeks and months to make it as complete as possible. The reason for stressing the importance of a detailed history is that, without it, the skin tests lose their value almost entirely. These two procedures must always go together.

IMPORTANCE OF SKIN TESTS

The skin test is an important procedure in pediatric allergy. It constitutes the second best approach in diagnostic pediatric allergy problems. Walzer[50] claims that the skin test has been the most important single influence in the development of the subject of allergy. Ratner[34] contends that without the benefit of skin tests the treatment of allergy would not have made the strides it has. Glaser[14] states that testing is necessary because it often gives aids which are time-saving and of great help in the conduct of the case. Feinberg[11] believes that allergic diseases cannot be successfully managed at present without the use of such tests. Peshkin[32] states that with the introduction of skin tests as a means of determining causal factors of certain allergic entities, the clinical approach to the study and treatment of allergy was placed on a rational basis. It can be generally stated that skin testing is a useful

tool which frequently points to the cause of symptoms. The procedure is of definite aid in the allergic work-up. During the past years the improvement in technique, the improved methods of preparation of extracts and a clearer understanding of the interpretation of reactions have served to increase the value of skin tests. They remain the most effective diagnostic laboratory procedure in most allergic disorders. Skin testing is considered imperative in diagnosing allergies in children.

Although the importance of the skin test is fully appreciated, its drawback and limitations as a diagnostic procedure in pediatric allergy must be pointed out. These are well known to all allergists. Skin testing is a laboratory procedure, and, as in all laboratory procedures, considerable experience is needed for effective interpretation of the results obtained from them. Experience has shown that skin tests are of tremendous value in some allergic conditions and either of limited value or completely useless in others. In any case, their value is dependent upon the clinician's ability to correlate the tests with the clinical history. The conclusions reached from them must be reasonable and must reflect sound clinical judgment.

TYPES OF SKIN TESTS

The most important skin tests in a specific diagnostic survey are the following: the scratch test or dermal test, the intracutaneous or intradermal test, the passive transfer or indirect method of testing, the patch test. The so-called puncture or prick test[17] is merely a modification of the scratch test.

It is important to know when and how to use these tests to obtain the greatest amount of information. For atopic conditions (asthma, hay fever, perennial nasal allergy, urticaria, angio-edema, eczema, and so on) the scratch and intracutaneous tests are used. The passive transfer test is used for the same conditions when direct testing is not possible. The patch test is not used in atopic conditions, but as an aid in contact allergy. The passive transfer and patch tests will be discussed below in more detail.

"Do Scratch Tests First"

Scratch and intracutaneous tests are the most important tests for atopic conditions. Some clinics use only the scratch test. Others rely entirely on the intracutaneous test. Today the fields of usefulness of each are well recognized. By far the majority of pediatric allergists have found a combination of the two methods the most desirable. The history should always precede skin testing, since it frequently provides advance warning of any peculiar or unusually pronounced degree of sensitization

to allergenic substances. By omitting these strong reactors, the scratch test can then be performed with the greatest safety. In diagnostic procedures I always perform the scratch test first. With proper technique it is better accepted by small children, who usually dislike the hypodermic needle. I will discuss the advantages and disadvantages of this test in more detail below. It is sufficient at this point to say that the scratch test will make many diagnoses, but it is not nearly as sensitive as the intracutaneous test. Many children with allergy will react only by the intradermal route of testing. A patient cannot be regarded as a negative skin reactor if reliance is placed entirely upon the scratch test method.

The intracutaneous test has one serious major disadvantage—the danger of constitutional reactions. These may be so serious as to cause sudden death.[18] All the deaths reported from diagnostic skin testing occurred when intracutaneous tests were performed without prior scratch testing. I feel that this is so important that I emphasize that *an intracutaneous test should never be done without first obtaining a negative scratch test for that substance.*[44, 47] "Do scratch tests first" should be the imperative procedure, not only for all general practitioners and pediatricians, but for experienced allergists as well. This procedure has the added advantage in that, when scratch tests are done first, stronger concentrations than are ordinarily used for intracutaneous testing can be used, and the diagnostic program is thereby benefited. Utilization of the safety factor of the scratch test and the greater sensitiveness of the intradermal test provide the examiner with the most favorable diagnostic approach to pediatric allergic conditions.

The Scratch Test

The technique is simple, but its details vary. Every allergist has developed his own favorite technique, has become expert in its use and has found out for himself the easiest and most reliable method for obtaining optimum results. I think that it is a matter of each of us choosing the method we are most familiar with and then becoming expert with that particular method. My own preference is for the method that accomplishes its purpose easily, quickly and with a minimal degree of emotional upset to both child and parent. A complete description of the technique on scratch tests may be found in any of the standard textbooks on allergy. Briefly, it is as follows:

The skin is washed with alcohol and allowed to dry. Superficial scratches are made in the skin with one's favorite instrument. This may be an ordinary darning needle or small scalpel. Other instruments used for this purpose are the Hill scarifier,[19] small lancets, hypodermic needles, cataract knives and the Morrison microscratcher.[28] It is recommended that the instrument used for scratch testing be properly sterilized before use on each patient to prevent the possibility of accidental transfer of serum hepatitis

infection. The choice of the site may be the back, upper arm, forearm or abdomen. My choice is the back or upper arm. The scratch should be either round, as produced with certain instruments, or linear, but not over 3 mm. long. It is important that it be deep enough to incise the epidermis, but it should never produce bleeding. Scratches are placed at least an inch apart. The allergens applied may be either in powdered or liquid form. Many prefer dry powdered allergens because they remain potent for at least 2 years. For the physician with a limited allergy practice it is economical and convenient to use the dry allergens. The powdered or liquid allergens are applied to the scratched areas. With powdered allergenic extracts apply 1 drop of tenth-normal sodium hydroxide to the scratch, and a pinhead-sized quantity of the allergenic powder is mixed with it, using the flat-tipped end of a toothpick. With liquid extracts apply 1 drop of the extract with the dropper-cap supplied with the bottle containing the extract. Positive reactions are usually evident within 5 to 30 minutes. A positive reaction is one greater than the control. It consists of an urticarial wheal with surrounding erythema and usually accompanied by itching.

Generally, the reactions in infants and young children are not as large and typical as those in older children and adults. The wheal is frequently lacking. The younger the patient, the more likely a flare or area of erythema will occur instead of a wheal. *Erythema may be the sole evidence of a positive reaction.* Because of these atypical skin responses, it is best to read the tests every 5 minutes over a period of 20 to 30 minutes rather than just once after a specified time, say 20 minutes. In this way those reactions which develop and fade rapidly are not missed. A reaction should be recorded when it reaches its peak. In infants and children this varies considerably with different patients with the same extract and with different extracts on the same patient. I wish to stress that in infants and children it is important to record slight reactions. I have found by experience that these borderline reactions to scratch tests usually show up as distinctly positive reactions by the intracutaneous method.

Borderline skin reactions by any method are important and are likely to be fully as indicative of the presence of clinical allergy to that substance as a strong reaction. Vaughn,[48] reporting on a series of cases, found borderline reactions in 47 per cent. He concluded after careful study that they are just as important in clinical significance as frank reactions. This point is especially important in the interpretation of skin reactions in infants and young children. It should always be remembered that every skin test recorded as positive, whether strong or weak, is subject to clinical interpretation based on past and present history and future course. It is a guide to treatment only after adequate and experienced clinical evaluation. This frequently shows that a skin reaction of mild or borderline sensitivity is more important than a large reaction recorded as four plus.

Advantages and Disadvantages. The advantages of the scratch test are as follows: (1) It is simpler to apply to infants and children. (2) It requires little equipment. (3) It is readily accepted by most infants and children since the discomfort is less. (4) The materials are easy

to preserve and remain stable. (5) Fewer sterile precautions are necessary. (6) Many tests may be performed at one time. (7) Falsely positive reactions are few. (8) Safety: There is little or no danger of causing a systemic reaction. (9) It eliminates the necessity for doing many intracutaneous tests, which are generally disliked by children. Frequently the scratch tests impart so much information that intracutaneous tests are not necessary. (10) It enables one to use stronger concentrations for the intracutaneous tests when the scratch tests are negative, thereby benefiting the diagnostic study. (11) It enables one to use fresh or frozen material for antigens of substances which are so unstable that extracts prepared by the usual techniques rapidly become impotent.

The main disadvantage to the scratch test is the lesser degree of sensitivity. In general, one can say that the scratch test is 100 times less sensitive or reactive than the intracutaneous test. However, if only one method of testing is used, this method should be the scratch test. It is definitely the method of choice for the general practitioner.

The Intracutaneous Test

The reader will find a complete description of this test in any standard textbook on allergy. Briefly, the technique is as follows:

The skin is cleansed with alcohol and dried. My preference for site is the outer aspect of the upper arm. I believe that intracutaneous tests should always be done on the arm or thigh where a rubber tourniquet may be effectively applied to prevent further absorption of antigen in case an excessive reaction occurs. When prior scratch testing has been done, reactions are unlikely, but it must be remembered that errors may occur in scratch testing. Sterile extracts and equipment must be used. As I never do an intracutaneous test before obtaining a negative or borderline scratch test, I use dilutions stronger than ordinarily used—the strongest available dilution which will not give a nonspecific, irritative falsely positive skin reaction. The test is made by injecting into the skin about 0.01 to 0.02 cc. of the extract. As a control a similar injection is made with sterile normal saline or diluting fluid in a nearby site. I wish to stress the importance of making these wheals as small as possible: the smaller the wheal, the more trustworthy are the results of the tests. I usually do about 6 to 12 tests at one sitting. These are spaced about 2 inches apart. When properly performed, the technique is practically painless. In reading the results of the tests I have adopted the same principles as with recording scratch tests—observing the reaction sites at 5-minute intervals over a period of about 20 minutes and giving due respect to borderline reactions.

Advantages and Disadvantages. The chief advantage of the intracutaneous test is greater sensitivity. This is important in pediatric allergy, since many patients are in the earlier stages of the development of allergy. In these early stages scratch tests are frequently negative. As stated above, skin tests in infants and young children cannot be regarded as reacting negatively until after failure to obtain positive reactions with extracts of proper strength by the intracutaneous route.

The disadvantages of the intracutaneous tests are as follows: (1) The

technique is more difficult. (2) The materials are more difficult to preserve—the need for refrigeration and storage space. (3) Greater sterile precautions are necessary. (4) The tests are not readily accepted by children because of their fear of the hypodermic needle. (5) More equipment is needed—a large supply of syringes and sharp needles. (6) Fewer tests can be performed at one time. (7) The diagnostic work-up is more limited because of fewer tests. (8) The danger of systemic reactions.

Fatalities have occurred with this type of testing. Because of this danger in inexperienced hands, the novice should restrict himself to the use of the scratch test technique.

The Passive Transfer Test (Prausnitz-Küstner Test)

This test is used when it is impossible or too difficult to perform skin tests on the patient directly. Pediatric allergists have so perfected their technique in the handling of infants and children that they seldom have to resort to this type of testing solely because of obstinacy or timidity on the part of the patient. Formerly the test was used frequently when little normal skin was available, as in infants and children with generalized eczema. Now many allergists prefer to clear the skin first with the systemic use of steroid drugs and test the patient directly. Likewise patients with chronic intractable asthma can be controlled with steroids instead of antihistaminics or sympathomimetic drugs and tested directly. The steroids, it appears, do not influence the results of skin testing as do the antihistaminics and sympathomimetic drugs. Whether this procedure will remain the accepted one remains to be seen, for the early introduction of steroid drugs presents certain problems. It is exceedingly difficult to stop the use of these hormones when once started, and such therapy materially increases the difficulty of treating these patients along conventional lines. The passive transfer test is used when the skin is definitely abnormal from nonallergic diseases in severe illness or in circumstances which prevent the patient from visiting his physician. The various indications for passive transfer tests have been enumerated by Walzer.[51] The technique of the test is more involved than other methods of testing and requires considerable experience for its proper performance. Briefly, the procedure is as follows:

Blood is drawn from the patient to be tested and the serum drawn off. After passing appropriate sterility tests, the serum is injected into another person into a series of sites. The recipient must be a normal nonallergic person, preferably a young adult. About 0.05 to 0.1 cc. of serum is introduced in each site, and the tests are done 1 to 4 days later. By intracutaneous technique the allergens to be tested are injected into these sites. Each test on a sensitized site is controlled by a similar one in a corresponding anatomic site of the skin which has not been treated with serum. A positive reaction is one larger than its control when read at the height of the reaction. These tests require the same degree of interpretation as the scratch and intracutaneous tests.

INTERPRETATION OF SKIN TESTS

The following discussion applies to all three types of tests described above: the scratch test, the intracutaneous test and the passive transfer test. The patch test, which is used almost exclusively for diagnosis in contact allergy, will be discussed below. The most important function after the performance of tests is their interpretation. The interpretation and evaluation of the results of skin tests require more specialized ability and judgment than performing them. Skin tests, as stated before, have definite drawbacks. One may obtain negative results for substances that cause clinical disease and positive results for substances that do not cause clinical disease. If a test shows negative for a substance known to be a factor for a clinical condition under investigation, this is known as a false negative test. If a test shows positive for a substance and one can show that it has nothing to do with the clinical condition under investigation, this is known as a false positive test. A positive skin reaction must be given proper interpretation. This will depend upon several factors, such as age of the patient, the clinical condition being studied, the substance to which the patient reacts, the season in which the patient reacts and the correlation with the clinical history. Thus it is important to know at the outset that a positive test does not necessarily indicate clinical sensitivity to an allergen which elicited it, nor does a negative test indicate an absence of clinical sensitivity to that allergen. The experenced physician realizes the probability in each case of a certain proportion of false negative and false positive reactions and, as will be pointed out, takes necessary steps toward their ultimate recognition. Skin tests are subject to clinical tests. Observation of the patient's response to elimination or reduction of exposure to the suspected allergen and, if possible, to re-exposure is the true test of the correctness of the interpretations based on skin tests.

False Positive Reactions

A false positive reaction has no etiologic significance for the clinical symptoms under investigation. The test may be positive because of mechanical and technical errors, or it may be a true immunologic response—a reaction mediated by atopic reagins. Cooke[7] prefers to call the latter asymptomatic reactions rather than false, since they are true pseudopod wheal reactions and indicate, at least, a skin sensitization. Those positive cutaneous reactions which result from nonimmunologic causes inherent in the test extract, in the tested skin or in the technique used, are more frequent in the inexperienced operator, but become less frequent with experience and greater skill.

False positive reactions from all causes are enumerated as follows:

1. Trauma. The use of a dull or too thick needle, too deep a scratch, a struggling child, and so forth, may result in a traumatic wheal.

2. Poor Technique. Use of too large a volume for intracutaneous testing; injection of air into the skin, causing a "splash reaction"; scratches or wheals too close together. A falsely positive reaction may occur if test sites are too close together. A positive skin reaction too close to a nearby scratch or endermal test site will influence the latter, tending to make it positive even though it is actually negative.

3. Irritating Substance in Syringe. The syringe may not have been thoroughly cleaned and may have contained an irritant.

4. Contaminating Substance in Syringe. The syringe may have not been thoroughly cleaned and may have contained a trace of another allergen to which the patient is highly sensitive. Even after prolonged washing and boiling of syringes a trace of an allergen may remain.[38]

5. Irritating or Urticariogenic Substances in Extract. In the process of preparation of extracts for testing, many crude materials which are inherently irritating to tissues must be properly removed. Certain substances appear to have histamine-like substances as contaminants.

6. Dermographism. This results in all tests being reported as positive, including the control, since even the slight mechanical trauma such as the performance of any skin test results in a whealing reaction. The reactivity of the patient's skin must always be kept in mind. One child's negative reaction may be as large as a tremendously positive reaction in another patient. Feinberg and Friedlaender[12] demonstrated the usefulness of the administration of antihistamines before testing in the presence of dermographism. Some allergists will resort to the passive transfer test.

7. Associated Clinical Allergy. In evaluating skin reactions the coexistence of other manifestations of allergy must be taken into consideration. For example, the patient may need relief for asthma, but have certain minor allergies such as an isolated spot of eczema or a stuffy nose. A positive test for egg may be related to the eczema, but have nothing to do with the asthma. The positive skin reaction may not explain the clinical condition under investigation, but does explain some other, insignificant allergic symptom.

8. Genetic Relationship of Allergens. A positive skin reaction may be part of a group reaction to the same botanical group.[49] For example, the pollens of various grasses contain ingredients with an apparently identical allergenic effect. Tuft and Blumstein[45] showed that positive skin reactions to certain fish extracts in patients who never ate them are caused by a common antigen in the extract. Infants who have never eaten parsley may react to it because of its close genetic relationship to carrots. Similarly, there is such a relation between milk and beef and between chicken feathers, hen's eggs and chicken meat.

9. Past Clinical Allergy. There is no doubt that many of the positive skin reactions to foods in older children represent past rather than present sensitivity. In children with asthma who previously had eczema many of the positive reactions for foods are tombstones of past allergy and have no etiologic bearing on the present complaint of asthma.[20] It is important that the examiner give proper interpretation to these reactions. The final criterion of the significance of positive tests is clinical trial of the food. Often it is found that few are actually important in children. In my opinion positive tests for foods in older children are less likely to be of etiologic significance than in infants. In the final analysis a positive skin test to a food in the young infant is of much greater clinical significance than in the older child or adult. Also a positive test for a food is more likely to be of significance in atopic dermatitis, urticaria and gastrointestinal disturbances than in respiratory allergy. It was first believed that many of the positive reactions to foods represent negative clinical reactions due possibly to the resorption factor and that with the advance of age, allergic persons no longer absorb undenatured antigens as occurs in early life. However, it has now been generally accepted that the intestinal tract is permeable to unchanged protein at any age and that the protection acquired by the child against unaltered proteins as he grows older is immunologic.[15]

10. Future Clinical Allergy. In infants and children positive reactions for pollens frequently occur several years before the classic symptoms of hay fever develop. It is an established fact that clinical allergy may develop some time after sensitization of the skin has occurred.

11. An Unrecognized Allergic Clinical Condition. A positive reaction may have relation to some clinical symptom which either the patient or the physician does not recognize as related to allergy. Such symptoms are headaches, clearing of the throat, fatigue, tiredness, gastrointestinal disturbances,[13] feeding problems in infancy,[5] symptoms of the allergic tension-fatigue syndrome,[41] neurologic disorders[9] and so on. It is now well established that a definite clinical allergy may masquerade as chronic fatigue, psychoneurosis, recurrent colds, cigarette cough, sinus trouble, stomach trouble, catarrh, malnutrition, nervousness, neuropathic child, and the like.

12. Subclinical Allergy. It is at least theoretically possible that an allergic reaction may occur without demonstrable reaction on the part of the patient. Reactions below the threshold of clinical recognition are grouped together as subclinical. Thus a positive skin test without corresponding clinical symptoms may indicate a sensitization biologically and clinically still beneath the threshold value. In these patients symptoms may develop in later years after sensitization has increased.

At this point it may be well to point out that a positive scratch test,

a true, well marked immunologic positive test with pseudopods—even if false in the sense as described above—always has some value. It is an index of allergy. Positive scratch tests of this kind are rare in normal infants and children.[4] The reaction is definite evidence of the existence of the allergic constitution, and this may be helpful in the differentiation of allergic disease from other types of illness quite aside from the etiologic significance of the particular antigens.

Special Interpretation in Difficult Cases

Frequently either the patient or physician may incorrectly believe that a test is falsely positive owing to their incomplete knowledge of the scope of some allergens and the diverse manifestations and intricacies of allergic disease. The following observations may have decisive significance in some cases and must be taken into consideration when control of a patient's symptoms has been unsuccessful.

Certain allergens are effective only when they come in contact with a particular shock organ through certain channels. A child may have a large positive reaction to wheat and yet ingest wheat without difficulty, but may suffer violent asthma from inhalation of wheat flour. In evaluating all positive reactions to foods one must not overlook the fact that the skin test is in most instances made with the allergen in its raw state. Cooking, canning or preserving a food may render it harmless to a patient. A positive reaction to egg may not be of any significance when the food is eaten well cooked, but there may be no tolerance of it if it is eaten partially cooked or raw. Some investigators have reported tolerance of raw foods which excited symptoms when cooked. In some infants the skin will often react to foods which they have not yet ingested. In highly sensitive infants these foods may cause a clinical reaction by inhalation of their vapors or odors.[23, 25] The contact with a substance may be unnoticeably small. Egg-sensitive patients can eat the meat of a rooster, but may react to the meat of a hen unless the viscera are carefully removed immediately after it has been killed.[10] In some cases exposure to quantities so small as to defy any method of identification may produce reactions, and these may be maximal reactions.[24]

An infant may react to nuts by skin test. If he is breast fed, these food antigens would reach him through the breast milk if they were contained in the mother's diet.[36] In infants on the breast all foods the mother eats must be considered, and the infant's allergy will be improved when positively reacting foods are omitted from her diet.[30, 37] Infants and children fed cow's milk are receiving allergens which cows eat. Evidence has been presented to show that cottonseed and flaxseed[16] may be present in cow's milk in quantities sufficient to affect patients

sensitive to these allergens. Some positive skin tests for substances are etiologic factors only when properly reinforced. A positive test for tomato may mean nothing to Tommy, who eats it without symptoms. But in ragweed season, when Tommy's allergic load is heavy, ingestion of tomato makes his hay fever worse. A child with mild sensitization may have symptoms only intermittently despite constant exposure to a dog in the home. The asthma becomes clinically apparent only when precipitated by some secondary factor such as exertion, chilling or respiratory infection. Exposure to an antigen either by ingestion or inhalation may not evoke symptoms unless reinforced by fatigue, constipation, infection, nonspecific irritants, psychogenic stimuli, and so on.

Thus a serious difficulty in the interpretation of skin tests is presented by the fact that some are of significance only when the exposure coincides with other additive or synergistic influences as described above. A positive skin test does not tell us how much of the substance will cause a clinical reaction. Sometimes large exposures or the cumulative effect of repeated exposures is required to elicit the clinical reaction. The patient may be able to tolerate exposure to a small amount. No symptoms are produced if the amount of antigen to which a patient is exposed is below his particular threshold. The physician must always consider the devious routes by which an allergen may reach the shock organ. The contact may have occurred by an uncommon route of invasion. A child allergic to chocolate denied its ingestion, but had a reaction when a suppository was given containing cocoa butter. Spain[40] has reported that egg, beef, nuts, seeds, banana, citrus fruits, celery, white potato and other fruits and vegetables, especially in food handlers, may excite asthmatic attacks by contact with the skin. It is important that the physician acquaint himself with the environmental sources of all inhalants. It is now common knowledge that nearly every home can reveal some material derived from the hair of cattle, hogs, horses, sheep, goats and rabbits.

Because of the ever-present and multitudinous opportunities for occult exposures, it is important that the physician have extensive knowledge of the occurrence of all allergens. Without it the evaluation of skin tests is made more difficult. The known exposure of the patient to the offending allergen in its active form through the natural channel of contact and in sufficient concentration will often prove the validity of a positive skin reaction whose value has, on superficial examination, seemed subject to question. With some clinical problems the search for eliciting agents can be a highly individualized matter. These patients present problems so complex that they are beyond the scope of the pediatrician and general practitioner. They can be solved successfully only by an exhaustive search demanding the most exacting and scrupulous methods of examination and using the trained and specialized knowledge of an astute clinician.

False Negative Tests

If a test shows negative for a substance known definitely to be a factor in a clinical condition under investigation, it is known as a false negative.

The causes for false negative tests are as follows:

1. Use of Poor Technique. The scratches may be too weak or too strong or the inoculations too deep. Experience enables the expert to obtain positive reaction when negative ones are obtained by the novice.

2. Use of Poor Materials. The extracts may be improperly prepared or poorly preserved, the concentration too weak or otherwise defective. The degree of the specific reaction to an offending allergen is dependent in part upon the concentration of the active principle in the test solution. Certain allergens are not potent and must be used only with slight dilution. When testing with high dilutions and negative results are obtained, it is advisable to repeat tests with more concentrated solutions. Certain food extracts are unstable and deteriorate rapidly; for example, the antigens of shellfish and berries[45] are unstable, so that extracts prepared by the usual technique rapidly become impotent. A scratch test with fresh or frozen material results in positive reactions in many instances.[2, 3]

3. Use of Improper Method. Although I believe that the scratch test should always be done first, *this test is less sensitive and may result in negative reactions when positive ones are attainable by the intracutaneous technique*. Occasionally skin and mucous membrane sensitivity do not parallel each other. In some clinically sensitive patients the mucous membrane tests may be positive when skin tests are negative.

4. Use of Drugs before the Test. The use of antiallergenic drugs affects the reactions from skin test.[29] Epinephrine, ephedrine and the antihistamines are especially effective in inhibiting reactions. Aminophylline also inhibits reactions, but to a less extent. If full benefits are to be obtained from skin tests, every unfavorable influence upon them must be appropriately dealt with. Before applying skin tests it is important to discontinue these drugs for at least 24 hours before testing. These drugs may obliterate entirely a positive reaction. It is generally believed that the steroids have no inhibitory effect on skin reactions.

5. Presence of Clinical Reaction at Time of Test. Smyth and Bain[39] reported that severe clinical allergic reactions are accompanied by fluctuations in the antibody titer and that the skin may at least be temporarily refractory. Skin tests may become negative during or immediately after a severe allergic attack. Falsely negative or greatly reduced reactions are frequently observed while the patient has an elevation in temperature.

6. Improper Site. Testing in the least sensitive skin sites may mean

the difference between positive and negative reactions. Alexander and McConnell[1] call attention to the variability of positive response on different sites of the skin. My practice is to use the back for scratch tests and the upper arm for intracutaneous tests.

7. Nonreactive Skin. The skin may be dehydrated, atrophic or indurated. Other factors such as nutritional state, presence of edema and circulatory state may affect the reactivity of the skin. A temporarily nonreactive phase appears due to fainting or apprehension.

8. Dissimilarity in Chemical Structure between Testing and Clinical Allergens. This happens especially with foods. The offending substance may not be the food itself, but its derivatives formed by metabolic processes within the organism producing secondary allergens.[8, 47] Thus the allergen used for testing may not represent the form in which it is harmful to the patient. The dissimilarity in chemical structure may also occur with inhalant allergens. Attention is called to the work of Hooker[22] which showed that different breeds of dogs may give specific positive skin tests for that breed alone. Unless, therefore, the patient is tested with an extract of the dander of his own pet, a falsely negative test may result.

9. Improper Reading of Tests. The degree of skin reaction varies and in some infants and children may be slight. Failure to read reactions at the proper time or in the proper light will miss many positive reactions. Failure to appreciate the importance of borderline reactions in infants and children is another factor.

10. Imperfect Antigens. Drugs such as aspirin, sulfonamides, phenolphthalein, which produce characteristic allergic clinical reactions, never give positive skin reactions. It is believed that the drug must conjugate itself to some other substance, perhaps a tissue protein, to become antigenically active.

11. Different Mechanism. Skin reactions are negative in all conditions in which the reagin mechanism is not present. This is true in many cases of angio-edema, urticaria and in drug sensitiveness in which apparently a different antigen-antibody mechanism is in force.

Mistakes and Fallacies

Many of the mistakes and fallacies about skin tests have to do with their interpretation and have been enumerated above. Additional mistakes and fallacies are listed here, with some repeated for emphasis.

1. It is a fallacy to believe that skin tests are of no value in infants and young children. Tests can be performed at any age and are frequently of value even in infants under three months of age.

2. It is a mistake to regard eczema in infants and young children as caused only by what they eat.[21] Environmental allergens and con-

tact substances frequently are etiologic agents. Therefore tests with environmental allergens—both scratch and intracutaneous—and patch tests with suspected substances may be of great importance. Patch tests are done in atopic dermatitis when a superadded contact dermatitis is suspected.

3. *The presence or absence of skin test reactions is not the one deciding factor in establishing a diagnosis of allergy.* A patient may have negative tests both by scratch and intracutaneous methods properly done and yet have severe clinical allergy to such common factors as ragweed, house dust, animal dander and foods. The search for etiologic factors should not cease with skin testing. Other methods of specific diagnosis should be used. Attention must be directed also to agents producing sensitivity which can never be ruled out by negative skin tests. This applies to a large class of drug-sensitive cases and the abnormal responses to physical agents, chemical agents, heat, cold, light and emotional stimuli.

4. It is a fallacy to believe that the skin reaction can be used to determine whether the patient has lost his sensitivity to a substance. This is especially true with inhalants. For example, a patient may show a skin reaction to pollen 20 years after his clinical sensitivity has disappeared. Also, the disappearance of a positive skin reaction to a substance does not necessarily mean clinical tolerance to that substance. Such disappearance cannot be relied upon as a criterion of improved tolerance to permit readdition of foods.

5. It is a fallacy to believe that the skin test can be used as a dependable indicator of the degree of clinical sensitivity of the patient. Although, on the average, a large skin reaction indicates a greater degree of clinical sensitivity, there are too many exceptions to make this rule reliable. A patient with a low degree of sensitivity may exhibit severe symptoms if the amount of exposure is large. The skin test should be regarded as a qualitative, not quantitative, indicator of clinical sensitiveness.

6. It is a fallacy to believe that sensitivity remains fixed. As the child develops, new contacts are made. Thus new clinical and skin sensitivities may arise which were not present when the child was originally investigated.

7. It is a mistake to omit skin testing in difficult and recurring cases of gastrointestinal allergy, migraine, urticaria and angio-edema. Although skin tests are less likely to be of aid in these cases, positive reactions may occur, and they could be the means of pointing toward a practical and rapid solution of the case. This is especially true in dealing with the allergies of infants and children. The real treatment of these conditions is to remove the cause of the attacks. The persistence of the allergic tendency is of not the slightest consequence as long as the

attacks are warded off or indefinitely postponed. Thus the mere negative treatment by abstention from the exciting cause of the allergic attacks may amount to a virtual and final cure. If skin tests fail to reveal these causes, there are other methods of diagnosis, and the patient should not be denied the opportunity to be benefited by them.

ALLERGY TO DRUGS

It is generally stated that scratch and intradermal skin tests in drug allergy are useless. Practically all drugs give negative reactions by scratch or intradermal methods of testing. Parents must be asked about their child's ability to tolerate drugs, for as a rule the clinical evidence will be the only diagnostic proof available. Positive skin reactions may occur with endocrine preparations and tissue extracts. Some authors believe that skin testing with penicillin is a worth-while procedure.[27] Fatal reaction to the injection of penicillin is such a distinct hazard[6] that any procedure which will diminish it would be most welcome. Screening out in advance those patients giving an immediate positive skin test with penicillin is a step in that direction. However, the fact that a negative skin test with any allergen does not rule out clinical sensitization should always be kept in mind, lest the unwary be misled by the assurance that an injection of penicillin can be safely given if a preliminary skin test with it is negative. The question is frequently asked whether a skin and/or clinical sensitivity to the air-borne spores of fungi indicates a sensitivity to the drug penicillin. All the reports in the literature indicate that there is no correlation between skin tests with penicillin and those with antigenic mold spores, including the Penicillium mold. The drug penicillin is a product of growth of the mold *Penicillium notatum*. It appears that the drug contains little, if any, of the mold antigen.

DELAYED REACTIONS

A delayed reaction is an inflammatory reaction which occurs 24 to 72 hours after performing the scratch or intradermal tests. It is rare with the scratch test. It is frequent with the intracutaneous tests with bacterial antigens, vaccines or filtrates. Some allergists attach a great deal of significance to delayed reactions. Because of the uncertainty of their importance, they will not be discussed in this report.

THE PATCH TEST

The patch test is not used as a diagnostic procedure in atopic types of sensitivity. Its primary uses are for diagnostic aid in contact dermatitis

and occasionally in drug sensitivities. The technique of the patch test is completely described in any of the standard textbooks on allergy and dermatology.

Briefly, it consists in application of a small portion of the suspected material on a convenient location of the skin of the patient to be tested, covering it with an occlusive dressing and leaving the material in place for at least 48 hours. A similar patch without testing material should be applied as a control. A positive test is indicated by a dermatitis at the site of contact. It is recommended to observe the site for several days after removal of the patch to detect delayed reactions.

A complete list of substances, concentrations and vehicles to be used in patch tests has been compiled by Sulzberger and Baer.[42] It is essential that the concentration of the material used for patch testing be correct so that it will not react on the normal skin in the manner of a primary irritant. The patch test is used chiefly in those instances in which a contact factor might be suspected. In dermatoses of the contact type this test is the only one of value. Positive reactions are likely to be of clinical significance. Children with generalized rashes due to drugs taken systemically may show a positive patch test to the offending drug.

SUMMARY

The discovery and elimination of causal allergens have decisive significance in the management of allergic disease. This requires utilization of the various methods at our disposal for specific diagnosis. Skin testing together with a good history provides the examiner with the most favorable diagnostic approach to pediatric allergic conditions. The four most important tests are the scratch test, the intracutaneous test, the passive transfer test and the patch test. It is important for the examiner to know when and how to use these tests to obtain the greatest amount of information. The performance of direct skin tests in infants and young children requires special skill. Because the intracutaneous technique is considered dangerous in inexperienced hands, the novice should restrict himself to the scratch test technique.

The interpretation and evaluation of the results of skin tests require more specialized ability and judgment than their performance. It is important to appreciate that a positive test does not necessarily indicate clinical sensitivity to an allergen which elicited it, nor does a negative test indicate an absence of clinical sensitivity to that allergen. False positive reactions are common, and the physician must acquaint himself with their causes. The number of false negative reactions can be reduced by appropriately dealing with every unfavorable influence upon skin testing procedure.

Skin tests for drug allergy have many drawbacks and with few ex-

ceptions are practically useless. The patch test is of definite value in contact allergy, and positive reactions are usually significant.

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ASTHMA IN INFANCY

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This discussion is based on a study of the records of 124 private patients seen with asthma before the age of 2 years.

DEFINITION

Asthma, as the word is used in this article, is synonymous with the term "bronchial asthma," and indicates a condition of partial bronchial obstruction due to or associated with an allergic reaction in the bronchi. This reaction consists in edema of the mucous membranes, increased secretion, and spasm of the bronchial muscles.

The patient experiences a variable degree of dyspnea and discomfort with a prolonged wheezing expiration, and examination of the chest elicits musical sounds and usually rales.

ETIOLOGY

The capacity of the patient to develop sensitization is the most important element in the etiology. This capacity is an inherited characteristic. Some infants have many severe allergies, as shown by the presence of severe asthma, severe eczema and large positive skin tests, all occurring together in the same patient. Other babies have no demonstrable allergies, no eczema and a mild asthma. These are illustrations of the great variation in capacity to develop sensitization.

Contact with the allergen is necessary to produce sensitization, and this allergen may be a food or an inhalant. Glaser and Johnstone[3] have emphasized the possible ill effects of the early feeding of cow's milk to babies with an allergic inheritance (see also p. 901), and the presence of various dusts may cause sensitization and the development of asthma.

Infections, both chronic and acute, frequently initiate the first attack of asthma, and these include pneumonia, whooping cough and measles.

The nature of this reaction is not understood. There is some evidence that there is actually an allergic reaction to bacterial products, not an atopic reaction of the immediate type, but still a reaction of hypersensitivity. Most allergists are still uncertain, however, as to the mechanism by which the infection has its effect on the asthmatic process.

Emotional states undoubtedly influence the asthmatic symptoms in infancy as they do in later years. Presumably the fundamental cause is immunologic, and the effect of the emotional state is that of an additional stress which may at times be sufficient to produce symptoms (see also p. 657).

PATHOLOGY

The pathology of asthma in the first two years is of especial interest because it is relatively uncomplicated by chronic infection. Cases are reported by Unger,[7] Huber and Koessler,[4] Pratt[6] and others. The reports of these authors may be summarized as follows: There is a varying amount of emphysema. The bronchioles may be filled with dried and inspissated mucoid secretions which produce hard rubbery plugs that occlude the bronchioles and smaller bronchi. The bronchial mucous glands and the basement membrane are enlarged. The bronchial smooth muscles are thickened, more from edema and cellular infiltration than from hypertrophy. There may be hypertrophy or dilatation of the right ventricle of the heart.

INCIDENCE

Asthma in infancy is common. Bray,[1] using the published figures of many authors and including his own, found that of all cases of asthma in the first 10 years of life, 22 per cent begin in the first year and 17 per cent in the second year. There has been no reason to doubt this; every pediatrician finds that his cases of asthma frequently have their first symptoms before the age of two.

SYMPTOMS

The first symptom of asthma is likely to be an attack of wheezing with or following a "cold" or respiratory infection. This first attack, commonly called asthmatic bronchitis, is in infancy likely to persist, even for a month or two. The persistent wheezing is a characteristic of asthma at this age.

Even more striking is the characteristic of the wheezing during the first six months of life. During this period, in fully half of the cases, there is at first no sign of either the prolonged expiration or the musical

sounds. Instead there is a noisy bronchial rattle with coughing and sometimes much dyspnea. When these babies have a musical expiratory sound, it may be almost obscured by the coarse bronchial and tracheal rales.

These symptoms and signs in the young babies are often called croup, but there is no aphonia or hoarseness, there is no great inspiratory stridor, and the retraction above the clavicle is slight. The dyspnea may be accompanied with cyanosis, especially after coughing, but the whole impression is that the obstruction is due to fluid and semi-fluid in the bronchi. It may be that the general opinion that croup often precedes asthma is due partly to the frequency of unrecognized early asthma in little babies.

This early asthma, without prolonged expiratory wheezes and musical rales, is just as common as the more typical form during the first six months of life. In the second six months it is less frequent, and after the first year it is unusual.

In infancy the symptoms commonly occur with a respiratory infection, and usually seem to be caused only by such infection. Whether they are due only to infection is at least debatable; it is evident in many cases that the infants do much better in the hospital, presumably owing to the absence of inhalant allergens there; also it is evident that in later childhood many attacks that seem to be due entirely to infections are, in fact, largely caused by the underlying allergy such as ragweed, house dust or animal dander. However this may be, respiratory infections are prominent in asthmatic attacks in infancy.

When a baby is taken to a hospital with an asthmatic attack, it is common to have the x-ray film show an area of pneumonitis which clears up promptly with an antibiotic.

Almost always the asthmatic attack can be at least temporarily relieved in the hospital, but there is often a tendency of the wheezing to recur. Usually the symptoms can be gradually relieved by treatment, and most of these patients do very well. Some of them, especially the ones with many and pronounced allergies, tend to get worse and give the doctor a long and difficult problem.

DIAGNOSIS

The diagnosis should be made ideally by noting the recurrent wheezing, by demonstrating the allergic state, and by eliminating other causes of bronchial obstruction.

The recurrent or in some cases the continuous wheezing with prolonged expiratory sounds and with musical rales and rhonchi is the most important diagnostic feature. In some cases the recurrence of wheezing is so typical that it is almost pathognomonic. In many cases this is not

so; the rattling dyspnea, common in the first six months of life, may be due to one of many things, including recurrent infection, whooping cough, congenital anomalies of the respiratory tract, the esophagus or the aorta, foreign body in the bronchus, or pancreatic fibrosis. Continuous wheezing is an indication for careful study, as is any suggestion of localized signs in the chest.

The allergic state should be demonstrated if possible. The presence of atopic dermatitis, strongly positive scratch tests, eosinophilia in the nasal or bronchial secretions, or the clear-cut production of symptoms by exposure to an allergen gives reliable evidence. A history of asthma or hay fever in the father, mother or sibling, or the presence of a blood eosinophilia in the patient, is circumstantial evidence which is useful in backing up a doubtful diagnosis. In many cases it is impossible at first to show the presence of allergy; with these it may be necessary to delay the positive diagnosis while treating the patient appropriately.

The procedures for ruling out other conditions which might cause bronchial obstruction depend on the nature of the case. I believe that every patient should have an x-ray of the chest, a white blood cell count and differential, and a patch test for tuberculosis. The chloride plate test for pancreatic fibrosis, estimation of blood gamma globulin, x-ray studies with a barium swallow, and occasionally bronchoscopy, should be used promptly if the symptoms are continuous and do not clear up with treatment.

It seems to me that most of the doubtful cases turn out to be asthma, and that the best plan is to treat these as such, being constantly alert for other conditions until the diagnosis is definite. I have found only one unusual condition in a baby sent to me for asthma, and that was pancreatic fibrosis. Several times I have had patients with recurrent bronchitis or bronchiolitis in whom I found no signs of allergy.

Wittig and Glaser[8] have reported a series of patients with bronchiolitis, 32 per cent of whom later had asthma. This brings up the point that doubtless some of these patients belong in the group under six months of age that I am reporting as asthma.

PROGNOSIS

The ultimate prognosis of asthma in infancy is, on the whole, probably about the same as in later childhood; many of these patients clear up rapidly with treatment; the worse ones are likely to clear up in their teens. These general statements seem to be justified by the meager evidence available. (See also page 725.)

I have some definite evidence as to the more immediate outlook. Eighty-seven patients were followed up for an average of seven years. Of these, 55 per cent had done no wheezing at all during the last year of follow-up, and 43 per cent had done at least some wheezing.

Two patients had died, one from a severe respiratory infection, and one under unknown circumstances. This may be in line with larger series; the death rate from asthma has been shown to be small in childhood and is probably equally small in infancy. The death rate may increase when cortisone or related compounds are used for extended periods.

The course of asthma in certain groups of babies is interesting and instructive. Nineteen of the infants had asthma, definitely positive skin tests for egg, and atopic dermatitis. In this group the prognosis for early recovery was bad. Sixteen of the 19 are still wheezing, at least to the extent of some wheezing during the last year; 2 after a prolonged illness are now not wheezing, and only 1 had a fairly good course with recovery at 11 years. Among this group of 19 were several of the most severe and intractable cases I have seen. It is evident that babies with asthma, atopic dermatitis and positive egg tests, all three at the same time, are likely to have severe asthma and have a serious time with it.

There were 12 asthma patients who had or had had what was believed to be atopic dermatitis, but had negative skin tests to egg. Of these, seven are well and five are still wheezing. These small figures may suggest that eczema without positive egg tests is not of such bad prognostic import.

There were 30 patients who had no atopic dermatitis and had entirely negative skin tests. Of these, 21 were not wheezing at the last report and 9 still had symptoms to the extent of some wheezing during the year. Apparently the prognosis in asthma is much better when there are no other signs of allergy.

All this would seem to indicate that the capacity to develop hypersensitiveness varies in degree. Under this supposition patients with the three manifestations of allergy developing at an early age have the greatest degree of sensitivity and the greatest number of sensitivities, and have the most difficult time. The infants with asthma, but with negative tests and no dermatitis, have the least degree of sensitivity and the fewest sensitizations, and thus usually have the easiest time and the best outlook. Although there are exceptions in both groups, this conclusion would seem to be valid.

TREATMENT OF THE ASTHMATIC ATTACK

The attack in infancy is usually induced by a respiratory infection. It may be violent with severe dyspnea, but much more frequently there is coughing, wheezing and some dyspnea without much anoxia or signs of great distress. Generally there is some fever and leukocytosis. As often as not the x-ray film will show some pneumonitis. Epinephrine gives some relief, but other sympathomimetic and antihistamine medications

are of little help. This wheezing gradually improves, but may persist to some degree for weeks until the next attack occurs. If it clears up in the hospital, it may recur within 48 hours after the return home.

With this kind of attack the most important medication is the use of antibiotics by mouth, if retained, by injection if there is vomiting. Epinephrine, 1:1000, 0.1 to 0.2 cc., is given once or twice; if it gives appreciable relief, the effect can be continued by giving Sus-phrine, 0.1 or 0.2 cc. every 6 hours.

Dehydration tends to develop in any severe asthmatic attack, and thus the administration of fluids becomes of prime importance. An intravenous drip of 250 cc. of 5 per cent dextrose solution may do the baby more good than anything else we can do; it not only keeps the bronchial secretions more liquid, but also keeps up the vitality. A subcutaneous infusion has the same result, but is more painful.

To get the intravenous drip, the baby must go to the hospital, and this is the best place anyway for a baby with a severe attack. An attack of asthma clears up more quickly in the hospital, owing partly to absence of the dust of home, partly to the better treatment that can be given there, and possibly partly to the change in emotional atmosphere.

Oxygen has its place in treatment. If the baby is anoxemic or badly exhausted, oxygen is of value. If the baby is not anoxemic and is just uncomfortable, the oxygen tent does not help him. Oxygen alone is an antiexpectorant and should always be used with added moisture. The use of an oxygen tent may frighten the patient and make him worse, and the tent makes good nursing difficult. In practice it has seemed to me that these babies usually are more comfortable and do better without oxygen.

It is also reported that in severe dyspnea the carbon dioxide in the blood may be much increased; that oxygen administration by lessening the breathing effort may exaggerate this condition; and that a dangerous acidosis may follow. I have had no personal experience with this difficulty.

Potassium iodide, 0.1 to 0.2 gm. three times a day, is usually given. Ephedrine by mouth may be substituted for epinephrine by injection as the patient improves. Aminophylline is a useful drug, but causes vomiting at times, usually because the dosage has been too large. Probably 0.12 gm. in 0.25 liter of dextrose solution is a good routine, but should not be given if there is any vomiting, and never more than twice in 24 hours. The aminophylline suppository or solution given by rectum is useful in less severe attacks.

MANAGEMENT OF THE ASTHMATIC INFANT

Management of the asthmatic infant depends to a large extent on the severity of the case. If the baby has recurrent wheezing, atopic derma-

titis and positive skin tests, the condition is serious, and every possible measure should be taken. If, however, there is no dermatitis and no positive skin test, and the wheezing is mild and not of long duration, we can be content with less stringent measures.

In discussing the pathology, the symptoms and the diagnosis, I have tried to be factual and to state what seems to me to be definitely known. When we come to treatment, this is more a matter of opinion. Treatment of babies with asthma varies widely in different clinics and with different allergists. I can only say what seems to me to be good treatment. In this discussion we shall consider first the baby that has a serious recurrent or continuous asthma.

We assume that a careful history has been taken and that a physical examination has been made. The next procedure is the skin tests.

I believe that some skin testing should be done in all cases. In the serious case that we are discussing, about 40 tests could be done, including the commoner pollens and inhalants and the foods in the infant's diet. These are scratch tests; intracutaneous tests may be done later if it seems desirable. The tests, if positive, confirm the diagnosis of the allergic state, they may help in the treatment, and positive tests, especially to egg, indicate that the baby has a serious capacity to develop sensitization.

The inhalant allergens to which the baby gives positive skin tests should be eliminated as far as possible; this includes especially animals and house dust. Even if the tests are negative, I should not want a cat or a bird in the house; the dog is sometimes so much a member of the family that he needs special consideration. Moderate measures to diminish wool, feathers and house dust should be carried out in the bedroom (see also p. 738); and we are governed by the particular indications of the case in the treatment of the living room.

In the serious case that we are considering, careful elimination diets should be tried in such a manner that we can compare periods without and with milk, cereals and other foods. Egg is usually not given. The skin tests may give us some valuable information, but the trial diets are a necessary part of the study to determine the diet for treatment. Freedman[2] has found that foods do not commonly produce asthma in children, but in babies under two, with the type that has many sensitizations, foods are often an important factor.

Injections are an essential part of the treatment. The material is a solution of the allergens to which we think the baby is sensitive and which are causing the symptoms, and usually we include bacterial vaccines.

In the procedure as outlined it is unusual to have anything like an anaphylactic reaction in a baby (I have never seen one), but it is common to make the wheezing worse, especially in the severer cases. To

avoid this unfavorable reaction, the injection to start with should be very weak; I commonly start with a 1:100,000 solution of house dust and a 1:1000 dilution of the stock or autogenous vaccine. The injections may be given once a week for 8 or 10 doses, and then the interval may be lengthened to 2 and then 3 weeks. When the baby is doing well and a sufficiently large dose is reached, this may be repeated once in four weeks.

Medication as in older children may be given in appropriate doses. Antibiotics are of value in acute respiratory infections, but I have not been impressed by their continued use as a prophylactic measure. If the wheezing is not readily controlled, admission to the hospital, where we can not only relieve the wheezing, but also further study the patient by testing and by diets, seems to be the best course.

It is true that cortisone and related compounds will almost always control the symptoms and temporarily improve the condition of the patient, but they do not seem to be useful in the long run; there is some evidence that they lower the patient's resistance, not only to infection, but to shock and illness in general, and this lowered resistance may persist for six months after the steroids have been stopped. There is a growing belief among pediatricians that there is a rising death rate from asthma and that this rise is due to steroid therapy.

Homes for asthmatic children, whether in Denver or Tucson or in the seacoast districts of the Northeast, have been successful. Children sent to these homes are usually of the so-called intractable type with chronic asthma that cannot be properly controlled at home. It is astonishing that usually the wheezing either suddenly or gradually stops after the child has been admitted to a home. There seems to be no doubt that the physical environment with change of inhalant allergens is an important factor, and it is difficult to evaluate the emotional factors involved in separating the child from his home and parents.

These same factors seem to affect asthma in infancy. A baby will usually stop wheezing in the hospital much more quickly than he would at home. It is common for the wheezing to begin again when the patient goes home. This improvement in an institution can be utilized from time to time in severe cases with great benefit. Some hospitals have convalescent departments that are less expensive than the regular wards, and, if necessary, these patients can be left there for prolonged periods.

SUMMARY AND CONCLUSIONS

Asthma in infancy differs from the disease in older children in the following respects:

In the etiology respiratory infection plays a more important role.

In the first six months of life especially, the symptoms seem to be

more of secretion than of edema, and the respiratory noise is more of a rattling than an expiratory wheeze. During the first year there is more of a tendency to continuous wheezing with exacerbations, and less tendency to have normal breathing between attacks.

Differential diagnosis is sometimes a complicated problem, and the following conditions must be considered: recurrent infection, whooping cough, congenital anomalies, foreign body in the bronchus, pancreatic fibrosis and agammaglobulinemia.

The prognosis, taking this group as a whole, is probably about the same as that of the cases first seen in later childhood. I believe that the outlook in those cases which begin after the age of two would be better. The prognosis for early relief is not good when the patient has asthma, atopic dermatitis and positive scratch tests. The prognosis is usually excellent when the asthma is not too severe and there is no atopic dermatitis or positive scratch tests.

In treatment of the attack, antibiotics in the presence of infection, epinephrine, and the prevention of dehydration are emphasized.

In the management of the asthmatic baby, elimination of inhalant and food allergens, prevention and control of infections, and immunization injections are the principal measures. It is important to treat the baby before he becomes the child with intractable asthma.

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HYPOSENSITIZING (IMMUNIZING) INOCULATIONS IN HAY FEVER AND ASTHMA

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The injection treatment of asthma, hay fever and other allergic diseases is a method of increasing the tolerance of a sensitized patient for the causative allergens by a series of injections of such allergens in carefully increasing, graded doses. It is generally recognized that such inoculations do not reduce the sensitizing antibody (reagin), but, as a matter of fact, sometimes even produce an increase in this antibody.[20, 30] The only other known immunologic change which occurs as a result of injection treatment is the development of a blocking antibody.[11] Not too much is known of the mechanism by which the blocking antibody prevents allergic symptoms, if indeed it does. Mechanisms of immunity other than a blocking antibody may be involved and may indeed be more important than the blocking antibody. So far no studies have proved the presence of an antibody quantitatively related to the injection of pollen extract or related to levels of clinical protection. It is well known, however, that patients are improved clinically by injections of allergens to which they are sensitive, despite inadequate knowledge for its basis in immunology. The terms "hyposensitization" and "desensitization" are well entrenched in the literature of allergy, but it would seem that the process is one of immunization rather than hyposensitization or desensitization.

Such immunizing injections are usually given chiefly for inhalant factors, such as pollens, dusts and molds. Cottonseed injections may be required for those patients sensitive to this allergen by inhalation.

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Occasionally patients require inoculations for animal danders. Rarely are such injections given for foods, but when sensitivity to wheat, milk or egg persists, immunization may be indicated and has been successful in our hands. Inoculation with bacterial vaccines, either stock and/or autogenous vaccines, is frequently of value.

POLLINOSIS

Indications for Specific Treatment of Pollinosis

Asthma due to pollen should be treated by inoculation as soon as the diagnosis is made, regardless of the age of the child. Seasonal hay fever alone, *if mild, especially in the very young,* can be treated with antihistamines and other symptomatic measures without serious risk, but it is important to keep the child under observation, since asthma may develop if patients are untreated.[14, 26, 34] At the first sign of increase in symptoms of hay fever or the development of lower respiratory tract symptoms, i.e., coughing and/or wheezing, specific treatment should be started.

Treatment of Children Giving Positive Skin Tests to Pollens, but Clinically Free of Symptoms

Many patients give positive skin reactions to pollens not producing symptoms. For example, typical weed pollen cases frequently react equally well to grass pollen or tree pollen. A small percentage of these children subsequently have symptoms during these other seasons. There is little in the literature on the question of treatment of pollen cases with pollens that react positively, but for which there is no clinical history of symptoms. Many allergists incline to the belief that the patient should be treated for the clinical symptoms that fit his history and that one should not treat positive skin tests. Some believe that if a patient requires treatment for any pollens, others to which he is exposed should be included in his treatment program.[3, 31] Beiderman[3] reported that 5.5 per cent of patients reacting to pollens have symptoms the following year to these pollens and that treatment before the development of symptoms prevented such symptoms completely in most cases, and in others only mild symptoms occurred. Glaser[15] states that he gives pollens, if the tests are positive, as a prophylactic measure to an allergic child only if receiving treatment by injection for other antigens.

The decision as to whether all positive-reacting pollens should be included in immunization treatment depends to a great extent on the method of treatment used. Those in the "small-dose" school of treatment could well include 30 or 40 pollens in a mixture without much change in their program of treatment. Believing in the "maximum tolerated dose" method,[21] I am inclined to treat only those pollens

which fit the clinical history for the reason that, in order to reach a high dosage, a much larger program of treatment is involved, as shown in Figure 1.

It is evident that for each preseasonal pollen treatment a fairly large series of injections is needed to reach a high dose. For this reason, because our program of immunization is so extensive and treatment is carried to fairly high dosage, we inoculate children for positive-reacting pollens, but with a negative history for these pollens, only when injection treatment is already being given with other antigens for perennial symptoms such as allergic rhinitis, asthma, urticaria, atopic dermatitis, and the like.

Parents should be warned, however, that the child shows positive reactions not related to his clinical history and that symptoms may begin during these other seasons at any time in the future. In order to avoid misunderstanding it is important to point out to the parents that should such symptoms develop, they are not the result of the injection treatments (since such a misconception is not uncommon).

Co-seasonal Treatment

There is little disagreement among allergists as to the question of co-seasonal treatment when a patient presents himself for relief for the

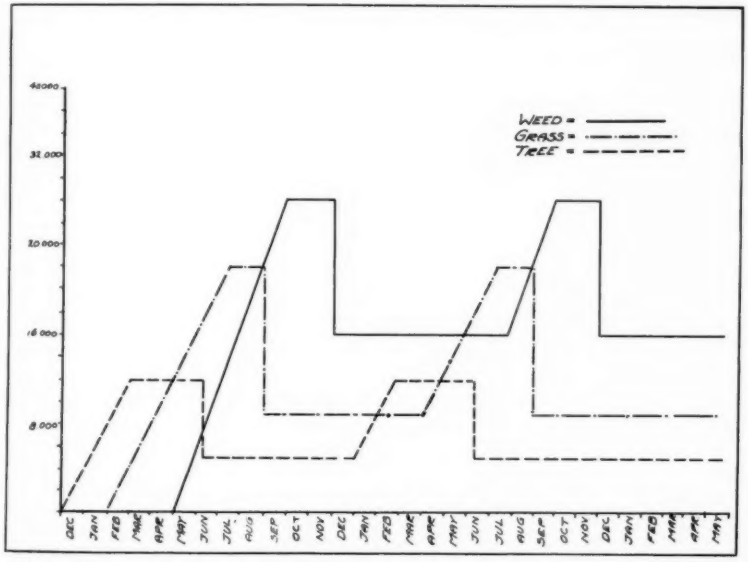

Fig. 1. Preseasonal, seasonal and perennial dosages for "average" triple-season pollen case.

first time during a pollen season. Most are in accord with the principle of very low dosage given intradermally. This method, advocated by Phillips[27, 28] and adopted with variations by others, including Hansel[16] and Rinkel,[29] has been effective in our hands.

The method consists in giving small doses of pollen extract intradermally at one- to three-day intervals. We administer for co-seasonal treatment from 0.01 to 0.1 cc. of the 1:10,000 dilution (100 units per cubic centimeter, 0.01 = 1 unit*), given intracutaneously at one- to three-day intervals. This dosage is raised or lowered, depending on the size of the skin reaction and the clinical results. In less sensitive patients it may be necessary to make intradermal injections with 1 per cent (10,000 units per cubic centimeter) or even 3 per cent (30,000 units per cubic centimeter) extracts in order to obtain a skin reaction and clinical relief of sufficient degree. Our best results seem to occur when the resultant wheal is about the size of a dime, not including the surrounding erythema.

TABLE 1. *Comparison of Methods of Labelling Pollen Extracts*

DILUTION WT./VOL.	PER CENT	NOON UNITS PER CC.	TOTAL NITROGEN MG. PER CC.	PROTEIN NITROGEN UNITS PER CC.
1:10,000	0.01	100	0.001	**64**
1:1000	0.1	1000	0.01	**640**
1:100	1.0	10,000	0.1	6400

100 protein nitrogen units equal approximately 150 Noon units.

Preseasonal Treatment

Much has been written about the top dose required to produce good results with pollen inoculations in children. In my opinion there are two main factors controlling the top dose. The first is the degree of clinical sensitivity, reflected only roughly by the degree of skin sensitivity; the second is the area in which allergy is being practiced. Undoubtedly, those who treat hay fever on the eastern seaboard and other low pollen-count areas can achieve good results with smaller doses, owing to the lower exposure to pollens in those areas as compared to other areas where the pollen count is often extremely high. Most allergists practicing in the mid-West find that the maximum tolerated dose

* The unit referred to in this paper is the Noon pollen unit, based on the weight-volume method of pollen extraction, which is the simplest method of preparing a reliable pollen extract. One gram of untreated, raw, dry, clean pollen is extracted in 100 cc. of extracting fluid. This yields approximately 0.1 mg. of total nitrogen per cubic centimeter and is arbitrarily labelled as containing 10,000 Noon units per cubic centimeter. In actual practice we make our extracts in 3 per cent concentration, i.e., 3 gm. per 100 cc. containing 30,000 units per cubic centimeter, or 6 per cent, containing 60,000 units per cubic centimeter, and make dilutions from these concentrates. Table 1 indicates the relationship between this unit and other commonly used methods of labelling extracts.

is the one that gives the best results. This concept, ascribed to Rockwell and quoted by Abramson,[1] has worked out best in our hands.

It is important to keep in mind that there is great individual variation in the size of the maximum tolerated dose. In general, the higher the degree of clinical sensitivity, the lower the top dose necessary to produce a good result. The degree of clinical sensitivity bears only a rough relationship to the degree of skin test sensitivity. This becomes obvious when one considers a ragweed pollen patient that reacts equally well by scratch test to both the grass pollens and the weed pollens, but gives a negative history of grass pollen hay fever. Such patients can receive large doses of grass pollen by injection without the slightest reaction. The same patient with the same size of reactions for ragweed and with a clinical history of ragweed sensitivity may be exquisitely sensitive to ragweed pollen by injection. In other patients small or negative scratch tests are obtained, yet the degree of clinical sensitivity may be high, and general reactions occur with minimal doses of pollen. In this group of patients a possible explanation is that the major portion of the sensitizing antibody is attached to the shock organ, and that only minor amounts remain in the circulation to react at the skin test site. (This theory is completely conjectural, however, and remains to be proved.) In only a general way, therefore, does the size of the skin reaction relate to the degree of clinical sensitivity. For this reason, titration of skin sensitivity by the method of serial dilutions intradermally, in our experience, is not a worth-while procedure for either adults or children.

We make no attempt to classify our cases rigidly according to this method as "A," "B," "C" or "D" types of clinical sensitivity.[12] On the contrary, we agree with Peshkin's[24, 25] contention that this procedure should be discontinued. It can be a misleading guide. We have adopted instead, for the past decade, a simple classification for pollen-sensitive patients, dividing them into two groups: those that react by scratch test to pollen, and those that do not. The scratch test is carried out by using a scarifier producing uniform scratches—one like that suggested by Hill.[17] A saturated solution of raw pollen extract in 50 per cent glycerin is applied to the scratches, which have been carried out as uniformly as possible. A number of typical cases of pollen hay fever and/or asthma do not react by scratch tests, but are clinically definitely sensitive. Our procedure is to follow a negative scratch test with an intradermal test, using 0.02 cc. of the indicated pollen extract, either a 1 per cent (10,000 units per cubic centimeter) or a 3 per cent (30,000 units per cubic centimeter) extract. Our patients are tested with the 1 per cent extract if any other pollen has reacted by the scratch method. If no other pollen has reacted by the scratch method, the 3 per cent extract is used for the intradermal test. When the intradermal test with these concentrations is made, one should observe the patient for a de-

layed reaction in 24 hours. A positive delayed reaction may be important clinically, since, in some patients negative to scratch tests, an immediate skin reaction to the intradermal test does not occur. We have rarely found a pollen-sensitive patient who failed to react positively to the 3 per cent pollen extract intradermally, either immediately or delayed. In patients in whom the 3 per cent pollen test is negative intradermally, a conjunctival test can be carried out. However, we have never seen a patient react to a conjunctival test who gave a negative reaction to a 3 per cent intradermal test. Those patients that react only by the intradermal test are classified as "B" cases of sensitivity.

Tables 2 and 3 indicate the approximate dosage schedules for patients in "A" and "B" groups respectively. The average child with pollinosis can tolerate approximately 0.5 to 1 cc. of the 1:33 dilution, equivalent to 15,000 to 30,000 pollen units. As an example of such dosages, in general a child of 5 years of age would receive 0.5 cc. of the 1:33 pollen extract as a top dose (15,000 Noon units). Children around 12 to 14 years of age would receive 1 cc. (30,000 Noon units) as the top dose.

TABLE 2. *Schedule of Pollen Injections for Patients Reacting to Scratch Tests (Group "A" Patients)*

DOSE	NOON UNITS	CC.	BOTTLE	UNITS PER CC.	DILUTION WT./VOL.
1st	5	0.05	No. 1	100	1:10,000
2nd	10	0.1			
3rd	20	0.2			
4th	35	0.35			
5th	60	0.6			
6th	100	0.1	No. 2	1000	1:1000
7th	150	0.15			
8th	250	0.25			
9th	400	0.4			
10th	650	0.65			
11th	1,000	0.1	No. 3	10,000	1:100
12th	1,500	0.15			
13th	2,000	0.2			
14th	3,000	0.3			
15th	4,000	0.4			
16th	5,000	0.5			
17th	6,500	0.65			
18th	8,000	0.8			
19th	9,000	0.3	No. 4	30,000	1:33 (3%)
20th	10,500	0.35			
21st	13,500	0.45			
22nd	16,500	0.55			
23rd	21,000	0.7			
24th	25,500	0.85			
25th	30,000	1.0			

This schedule is approximate for cases reacting to scratch tests. Initial and top doses will be lower for more sensitive patients.

TABLE 3. *Schedule of Pollen Injections for Patients not Reacting to Scratch Tests (Group "B" Patients)*

DOSE	NOON UNITS	CC.	BOTTLE	UNITS PER CC.	DILUTION WT./VOL.
1st	100	0.1	No. 2	1000	1:1000
2nd	200	0.2			
3rd	400	0.4			
4th	800	0.8			
5th	1,500	0.15	No. 3	10,000	1:100
6th	2,500	0.25			
7th	4,000	0.4			
8th	5,500	0.55			
9th	7,000	0.7			
10th	9,000	0.3	No. 4	30,000	1:33
11th	10,500	0.35			
12th	12,000	0.4			
13th	15,000	0.5			
14th	18,000	0.6			
15th	21,000	0.7			
16th	25,500	0.85			
17th	30,000	1.0			

This schedule is approximate for patients not reacting to scratch tests.

Local Reactions

The local reaction may be a good guide to increase in dosage, provided several of the fallacies involved in this conception are considered. Unless the antigenic material injected is deposited at the same depth under the skin each time, considerable variation in the extent of the local reaction can occur with the same dosage. As pointed out many years ago by Thommen,[10] the skin being the most reactive of the superficial tissues, the closer the injection is to the surface, the greater the local reaction. This can be demonstrated by administering the same dose of pollen extract to a patient on one occasion superficially and on another occasion intramuscularly, resulting in a larger local reaction in the case of the superficial injection and much less local reaction in the case of the intramuscular injection. In our experience, general reactions do not occur more commonly with intramuscular injections than with subcutaneous injections.[21] It has been shown that the absorption of pollen extract[19] and other injected material[22] is not invariably faster when given intramuscularly, but indeed may even be more slowly absorbed when given intramuscularly. For these reasons—greater reactivity closer to the surface and no more rapid absorption, nor increase in general reactions when the extract is given intramuscularly—we give all our immunizing injections intramuscularly into the triceps muscle.

Another common cause of local reaction is the use of extracts containing 50 per cent glycerin, which is an irritant. In small volumes

the amount of glycerin present may not produce much local reaction. Because we use fairly large volumes of pollen extract, from 0.5 to 1 cc. in children and even larger doses in adults, we have discontinued the use of glycerinated extracts for many years. We use pollen extracts prepared in a nonirritating alkaline 5 per cent dextrose solution, as evolved by Unger and Moore.[32] We have seen no mold or bacterial contamination of these extracts in the many years in which we have had experience with this extracting fluid.

Dosage of Pollen Extracts for Patients not Reacting by Scratch Tests

Because most patients not sensitive by scratch test can follow the schedule outlined in Table 3, many injections are saved in reaching a large dosage. It seems unreasonable that, after making an intradermal skin test with 200 or 600 units of pollen extract (0.02 cc., 10,000 units per cubic centimeter = 200 units; 0.02 cc., 30,000 units per cubic centimeter = 600 units), one should begin immunization with 5 units or less. For this reason we have adopted the schedule as indicated in Table 3 with fairly large increments. One should not follow either schedule arbitrarily. We have started patients on schedule "A" and after one or two injections mild generalized symptoms have occurred which indicated a high degree of sensitivity. Such patients should be restarted on 1:100,000 (10 units per cubic centimeter) or 1:1,000,000 (1 unit per cubic centimeter) extracts. We have treated a number of children whose maximum tolerated dose was from ½ to 1 unit. On the other hand, we have had patients who reacted well by scratch tests and therefore were started on schedule "A," who did not achieve good results unless they were carried to doses even higher than 30,000 pollen units. We have had similar experiences with patients assumed to be of "B" class sensitivity because they reacted only by a strong (1 or 3 per cent) intradermal skin test. On the first or second immunizing injection of 100 or 200 units, constitutional symptoms have occurred in occasional instances. Should this happen, the patient is immediately reclassified and treated as type "A" sensitivity. In general, one can say that any classification provides only a rough idea as to the degree of clinical sensitivity and reinforces a statement which has appeared many times in the literature to the effect that the size of the skin test reaction is not a true test of the degree of clinical sensitivity.

The dose of pollen extract necessary in children bears no relationship, except in a general way, to the weight and age of the child. Many children in our practice tolerate and require larger doses than some adults to achieve good results.

Preseasonal treatment should be begun long enough before the pollen season so that the estimated top dosage can be reached before the

pollen season. This may require one or two injections a week, depending on when treatment was started. We continue with the top dose once or twice weekly during the pollen seasons unless there is evidence that injections aggravate the hay fever or asthma. There is a small percentage of pollen-sensitive patients who are definitely made worse by receiving the top dose of pollen during the pollen season. In these patients we initially halve the dose. In rare cases it may be necessary to reduce the dose even further in order to avoid general reactions when the patient is exposed to pollen while receiving injections. We have never seen a patient in whom the injections had to be discontinued completely during a pollen season.

Perennial Treatment of Pollinosis

When the pollen season is over, we routinely halve the dose and administer the half-dose at intervals of every three weeks until about five or six weeks before the next pollen season. We then increase the dosage weekly until the top dose is again reached in time for the pollen season.

Patients Sensitive to More than One Pollen Season

We treat each pollen season separately, first increasing the dosage of the tree pollens if the patient is sensitive to this group, maintaining them at the top dose during the tree season, and lowering them to one-half during the rest of the year at a three-week interval. The same is done for the grass and ragweed seasons, as shown in Figure 1.

Pollen Mixtures

Pollens of plants which are closely related botanically are prepared in the same extracts. Thus we prepare separate mixtures of tree pollens, grass pollens and weed pollens. We are not in agreement with the practice commonly in use of preparing mixtures of unrelated pollens, since mixtures of immunologically unrelated allergens do not generally produce good clinical results in areas of high pollen counts. There are some patients exquisitely sensitive to pollens of one season and not as sensitive to pollens of another season. In order to avoid reactions from injections of such a mixture, one would need to use very weak dilutions for the entire group of allergens or prepare the mixture by using varying strengths of different pollen extracts. Mixtures of several unrelated pollen groups result in a proportionate reduction in the representation of any single pollen group in a given dose of the mixture. This would mean that the patient would receive only small amounts of the less

potent allergens for some of the pollen seasons. In order to increase the pollen dosage for any particular season, it would be necessary to carry along other pollens in the mixture beyond the time when it is necessary to keep the dosage for the earlier seasons at a high level. For these reasons we have found the administration of mixtures of unrelated pollen allergens to be generally unsatisfactory. However, when a child is being treated with several antigens, it is convenient to combine them in one or two syringes so that the number of injections can be lessened. This is usually done by drawing up the required dosage of each of the different antigens in the same syringe at the time of injection. This makes for complete flexibility in treatment. Should local or general reactions occur, one can readily detect which of the antigens should be lowered by the method of subtraction from or addition of the antigen to the mixture in the syringe. Our practice is not to give more than two injections to a child on the same visit regardless of the number of antigens mixed in the syringes being administered at one time.

Precautions after Pollen Injections

The same precautions must be followed after the injection of a pollen extract as for any other allergenic material. The patient should wait in the office for 20 minutes after each treatment. Epinephrine, 1:1000, must be available for immediate injection. The treatment of a general (constitutional) reaction and the precautions necessary to avoid such reactions can be found in all standard texts on allergy.

Our experience in using high-dose treatment is much the same as that reported by others, that the tendency to reactions occurs at the lower dosage levels, apparently before some degree of immunity is established. General reactions at the higher levels are much less frequent, provided proper precautions are taken as to vascular puncture. Many hundreds of patients have tolerated extraordinarily well the administration of these doses of pollen extracts with extremely rare general or local reactions even when all are administered together every three weeks during the winter months. During the past 10 years over 50,000 pollen injections have been administered to our clinic patients. During this period of time, epinephrine injections to overcome a constitutional reaction following pollen treatment have been administered 16 times, or at the rate of about one reaction per 3000 injections. General reactions in our private practice have occurred about as rarely. The infrequency of systemic reactions in our practice has not been the result of including in each injection a small dose of epinephrine, as others have advocated. We are not in agreement with the practice of routinely including small amounts of epinephrine in pollen injections as a method of avoiding reactions. Many children have extreme pallor, nausea, vomit-

ing and even shocklike symptoms as a result of even small injections of epinephrine. Ethylnorepinephrine hydrochloride (Bronkonephrine) generally does not cause such symptoms. For this reason, in order to lessen the tendency to reactions in those patients exhibiting extreme sensitivity, we prefer to incorporate in each antigen injection administered a small amount of an antihistaminic agent, with or without Bronkonephrine.

Repository Pollen Injections

Brown[5–9] and Loveless[23] have reported on the method of single annual inoculations of pollen emulsified in oil in the treatment of pollinosis. The method appears to offer great promise. We have had no personal experience with this procedure, which should await further investigation before general adoption.

IMMUNIZATION FOR OTHER SENSITIVITIES IN HAY FEVER AND ASTHMA

Molds

Other than pollen, the most frequently required inoculations are for molds and various dusts. If our patients react to molds by the scratch method, we begin with a 1:10,000 dilution and gradually increase the dosage by small increments over a long period of time in an effort to reach 0.1 to 0.2 cc. of the 1:1000 dilution. If the patient does not react by scratch test to molds, but does so with a 1:100 intradermal test, we begin with the 1:1000 dilution of mold and increase by small increments until the patient receives approximately 1 to 2 cc. of the 1:100 dilution. As in all hyposensitization procedures, one must be on guard against the development of general reactions, which, as in pollen immunization, tend to occur at the lower dosage levels during the initial stages of treatment.

House Dust

House dust sensitivity is a major cause of many allergic symptoms. It may be one of the causes of perennial asthma, allergic rhinitis, atopic dermatitis, urticaria, or a complicating factor in seasonal asthma or hay fever. We routinely test all allergic patients, whether seasonal or perennial, for house dust and have found Endo house dust effective and potent for both testing and treatment.

If a patient reacts to Endo house dust by the scratch method, using the 1:40 concentration (as supplied by the manufacturer), we routinely begin immunization with the 1:400,000 dilution, gradually increasing to 0.2 cc. of the 1:4000 dilution (1:40 diluted 1:100). If the patient

does not react by scratch test, but only by the intradermal test with the 1:400 dilution, we begin with the 1:40,000 dilution of Endo house dust and gradually increase to 1:4000. We have found that overtreatment with house dust is commonly the cause of poor results and have rarely exceeded the 1:4000 dilution of Endo house dust.

We routinely make autogenous house dust extracts on every allergic patient and have found this procedure advantageous and conducive to better results. In many instances the autogenous dust reacts much more strongly than Endo house dust or any of the constituents of house dust. Such large skin reactions frequently lead to a search for some item in the house to which the child is sensitive. By this means we have uncovered instances of such overlooked items. In the case of pets in the house, a much stronger reaction to autogenous house dust than to stock house dust material is a strong lever to use on the parents to eliminate a pet. Strong reactions to autogenous house dust have been valuable in enforcing better dust control as well as better pet control in the home. The administration of molds and house dust can be included along with pollen injection and/or other antigens, bacterial vaccine and, in some cases, animal danders when indicated.

Animal Danders

We have immunized children for feathers, cat, dog, horse, hog and cattle dander when exposure to these items was unavoidable. This is particularly true in the case of farm children, who may themselves be able to avoid such animals on their own farms, but are unable to avoid animal dander contacts on their friends' clothes or in the homes of their friends, or at school. We have also immunized children for animal danders, particularly the children of veterinarians, when contact was unavoidable. The occasion has also arisen to immunize children for dog dander when the psychologic effect of removing the dog from the home was so intense on the patient or other members of the family that a difficult emotional situation was created. Immunization of the patient with dog dander in some of these instances has been gratifying. At the same time we have used a silicone preparation (Allergex) to sponge the animal to diminish dander exposure.

We begin all treatment for animal dander sensitivity with very weak dilutions. If the patient reacts by scratch test to an animal dander, we begin with 1:1,000,000 dilution. If he reacts to animal dander only by intradermal test with a 1:1000 extract, we begin with a 1:100,000 dilution. In all instances, increments are made gradually, using stronger and stronger extracts until we reach a dilution of 0.1 or 0.2 cc. of the 1:1000 dilution for those that react either by scratch or intradermal test. Results in those cases which have required immunization for animal dander

have been satisfactory. The same objections mentioned above as to pollens apply to the use of the size of the skin test reactions to dusts, molds and animal danders as a criterion of clinical sensitivity. One cannot overemphasize the importance of proceeding with caution. One must not follow a schedule routinely, and one must be ready to revise such a schedule without hesitation.

Bacterial Vaccine

Upper respiratory tract infections precipitate attacks of asthma in many children. In some patients the attacks occur only in the presence of respiratory infection. One must not assume, however, that this is proof of the existence in any particular patient of bacterial allergy. Such infections may act as a triggering mechanism in a sensitized child able to tolerate his allergens except in the presence of a respiratory infection. There is actually no proof at present of bacterial sensitivity other than the reproduction of an attack of asthma as a result of an injection of a bacterial antigen. A number of methods have been evolved to detect bacterial sensitivity, but these are not universally accepted and are still in the experimental stage. The method of Blatt[4] seems to offer the most promise.

Not all allergists agree as to the value of bacterial vaccines, filtrates and toxoids in the treatment of asthma, asthmatic bronchitis, perennial allergic rhinitis and other allergic disorders. However, most allergists add bacterial vaccine empirically to other antigens in the treatment of these conditions in children despite variations in their enthusiasm for this procedure. Since treatment is being carried out with other antigens at the same time, it is difficult to evaluate the benefit derived from vaccine injections. Whatever beneficial effect it may have could result from (1) immunization against secondary bacterial invaders which frequently are associated with respiratory infections, (2) immunization for a true bacterial allergy (detectable only by production of symptoms with overdosage) or (3) a nonspecific effect (anamnestic response).

Our practice is to add stock respiratory vaccine routinely to our immunization program for children being treated for perennial asthma or perennial allergic rhinitis, whether attacks are predominantly associated with respiratory infection or not. It is best to make an intradermal skin test in advance of such treatment, not for the purpose of determining bacterial sensitivity, but for the purpose of determining a starting dose which will not produce a severe local reaction or a febrile effect. The size of the delayed positive skin reaction is a good index of the tendency to local and febrile reactions. Depending on the size of the delayed skin reaction, we begin with a 1:10, 1:100 or 1:1000 dilution (full strength is 100 million organisms per cubic centimeter).

For some children particularly susceptible to respiratory infections who do not do well after complete allergic studies and subsequent adequate immunization for the implicated antigens, including stock respiratory vaccines, we have prepared autogenous vaccines from the nose and throat. We are in agreement with Crump,[13] who states that in many children autogenous vaccines are superior to stock vaccines, particularly in the treatment of children whose asthmatic episodes are in the main associated with respiratory infections.

TERMINATION OF TREATMENT FOR ASTHMA AND/OR HAY FEVER

The problem always arises, when treating an allergic child, as to when the inoculations should be terminated. Our rule is that after one year of complete freedom from symptoms, using the perennial method outlined above, which includes in the injections all indicated antigens, we continue treatment at three-week intervals for an additional year. During this last year of treatment we do not increase the dose or decrease the interval before the pollen seasons. This requires approximately 17 injections for the entire year. If the patient is still free of symptoms, treatment is discontinued.

Our experience with high-dose treatment is that most children with hay fever and/or asthma can be given 80 to 90 per cent relief the first year of treatment and can stop treatment permanently in 50 per cent of cases in 3 to 5 years of continuous perennial high-dose therapy. The development of asthma in hay fever patients thoroughly treated rarely occurs. Asthma already present generally clears up as readily as or sooner than the hay fever symptoms. Patients exquisitely sensitive and unable to tolerate high-dose treatment obtain good relief, but "cures" require considerably more time, occasionally many years.

EFFECT OF INOCULATION TREATMENT ON SKIN TEST SENSITIVITY

Skin test reactions are not a criterion for "cure," but most patients on high-dose treatment who are symptom-free do show a diminution of skin test sensitivity.[2, 18, 33]

SUMMARY

The principles of hyposensitization (immunization) in hay fever and asthma consist in raising the patient's tolerance to substances to which he is sensitive. In order to accomplish this, the principle of administering the "maximum tolerated dose" has worked out best in our hands. The determination of this dose is not simple and is not always related to skin test sensitivity. We have classified patients by

dividing them into those that react by scratch test (group "A") and those that react by a potent intradermal test (group "B"). No classification can be rigid, since clinical sensitivity can be only roughly correlated with skin test sensitivity. Only in a general way can one assume that the higher the degree of skin test sensitivity the greater the degree of clinical sensitivity. The dosage for each patient must be determined by his individual reaction. The fallacies involved in utilizing the local reaction as a major guide to dosage have been pointed out.

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INFECTION IN BRONCHIAL ALLERGIC DISEASE

Bronchial Asthma, Allergic Bronchitis, Asthmatic Bronchitis

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The role of infection in respiratory allergic diseases can be best interpreted on the basis of the immunologic reactions involved, the tissue responses to these reactions, and the signs and symptoms produced by these tissue changes. All these factors serve to guide the clinician in the management of respiratory allergic diseases.

IMMUNOLOGY

In the present state of our understanding of the immune mechanism concerned in allergic diseases, accurate classification is difficult. In allergic disease of the respiratory tract it is necessary to consider two classes of allergic response, the atopic form of immediate reactivity and the delayed type of response. The place of such reactions as the anaphylactic type, the Arthus reaction and contact dermatitis is indicated in Table 4.

Atopic Allergy

In addition to its strong familial or hereditary tendency, atopic allergy has several important immunologic characteristics:

1. After application of an antigen to a scarified area of skin (scratch or puncture test) or after an intradermal injection (intradermal test) an immediate reaction characterized by a flare or wheal occurs. This

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TABLE 4. *Classification of Allergic Reactions**

TYPE I. *IMMEDIATE REACTIONS*—ASSOCIATED WITH CIRCULATING ANTIBODIES

1. *Precipitating antibodies*

A. Anaphylactic type
- Anaphylactic shock
- Serum disease

(1) Can be induced experimentally
(2) Heredity a negligible factor

B. Arthus reaction—a phase of the delayed type II reaction
(1) Can be induced experimentally
(2) Degree of reactivity directly proportional to circulating antibody titer

2. *Nonprecipitating antibodies* (demonstrated by passive transfer [P-K reaction])

Atopy
- Hay fever—Allergic rhinitis
- Bronchial allergic disease
  - Bronchial asthma
  - Allergic bronchitis
  - Asthmatic bronchitis
- Allergic dermatitis—Infantile eczema
- Urticaria
- Gastrointestinal allergic disease
- More rarely any organ of the body may be involved

(1) Cannot be induced experimentally
(2) Heredity an important factor†

TYPE II. *DELAYED REACTIONS*—ASSOCIATED WITH CELLULAR ANTIBODIES

1. *Noninfectious agents*—Plants and chemical substances serve as antigens

Contact dermatitis
- Dermatitis venenata (poison oak, ivy, sumac, etc.)
- Drugs and chemicals as contactants (mercury, nickel, etc.)

2. *Infectious agents*—serve as antigens (the tuberculin type reaction)
Bacterial
Viral
Spirochetal

3. Jones-Mote reaction[7,8]—Fleeting, delayed type of reactivity (frequently observed with insect bites)

* This classification may serve as a clinical guide. Exact classification is not possible in the light of our present understanding of the immune mechanisms.

† Although heredity seems to be an important factor in the incidence of atopic allergic disease, it is likely that the genetic factor is not an absolute one. Environmental influences may reproduce a situation usually identified with a genetic action.[15] This could be true in atopy.

reaction reaches its maximum within about 20 minutes and usually fades within 40 to 60 minutes.

2. Circulating or humoral antibodies are present. These are demontrable only by passive transfer (the Prausnitz-Küstner reaction).

3. There is increased permeability of vessels for fluid elements of the blood.

4. There is stimulation of smooth muscle.

5. A tissue culture of cells derived from a sensitized animal plus the specific antigen manifests no influence upon the cells.

6. This form of allergic response cannot be induced experimentally.

7. Pollen, foods and epidermal factors usually serve as antigens in this type of allergic response.

Delayed Allergic Reaction

Delayed type of allergy which is classically illustrated by the tuberculin reaction presents the following immunologic characteristics:

1. After application of antigen by either scarification or intradermal injection, no reaction is obvious for 12 to 24 hours. The lesion is characterized by induration and redness at the site of injection. In severe responses vesiculation or even bullous formation may appear, and at times even necrosis of tissues. After its appearance the lesion may persist for days or weeks.

2. No circulating humoral antibodies are demonstrable except in the Arthus phase, when antibodies are demonstrable by the precipitin test. The Arthus reaction is also manifested by an immediate type of skin reactivity and should be differentiated from the immediate whealing reaction of atopic allergy by the presence of precipitating antibodies in the blood serum. Depending upon the degree of blood vessel damage, the tissue response may vary from slight hemorrhage to necrosis and severe tissue damage. Recent observations in the field of immunology seem to indicate that the Arthus reaction and the delayed type of allergic response may be different phases of the same immune mechanism.[9, 11, 12] The delayed type of response represents an earlier stage; the Arthus type, together with the formation of antibodies, a later stage in the development of the sensitization process. In observations in our own laboratories on allergy to insect bites we have noted an immediate type of reactivity supplanting the commonly observed delayed reaction to insect bites (fleas, mosquitoes), which suggests a similar mechanism.[5, 6]

3. There is no effect upon blood vessels except in reactions of the Arthus mechanism.

4. There is no effect upon smooth muscle.

5. A tissue culture of cells derived from a sensitized animal plus the specific antigen produces death of cells.

6. This type of sensitivity can be produced experimentally in animals.

7. Bacteria or bacterial products serve as antigens. Under special conditions, as in conjunction with Freund's adjuvant, it is possible experimentally to induce a delayed type of reactivity with pollen, foods or epidermal factors serving as antigens. It is important to bear in mind that either bacteria, bacterial vaccines or autogenous vaccines, when injected intradermally for test purposes, manifest a delayed type of reaction when sensitivity is observed.[13] It is important to bear this distinction in mind in evaluating the role of infection in clinical allergy.

TISSUE RESPONSES IN ALLERGIC REACTIONS

In the *immediate atopic type* of reactivity the tissue changes are characterized by: (1) dilatation of vessels—the capillaries especially are involved. (2) Increased permeability of vessels. Here again the capillaries are the seat of involvement, permitting extravasation of the fluid elements of the blood which results in edema of either the tissues or organ involved by the reaction. (3) Contraction of smooth muscle. In the case of the respiratory tract this causes bronchospasm. (4) Stimulation of glands. In the case of the respiratory tract this causes an increased production of serous, seromucoid or mucoid discharge.

Note that with any one or any combination of these factors operating upon the tissues the resulting changes are reversible. No tissue damage occurs. When the process is arrested or controlled, there is complete restitution of tissues.

The wheal of urticaria serves as a common illustration. With control of the allergic reaction there is absorption of the edema fluid with complete restitution of the skin.

In the *delayed type of reactivity* the tissue responses observed are as follows: (1) Death of cells results in necrosis of tissues. (2) Destruction of blood vessels. In the Arthus reaction this results in hemorrhage and necrosis of tissues.

In either instance the end result is irreversible tissue destruction which differs strikingly from the benign reversible tissue responses caused by the edema and muscle spasm of the atopic immediate allergic response.

TISSUE CHANGES AND THE SIGNS AND SYMPTOMS OF BRONCHIAL ALLERGIC DISEASE (BRONCHIAL ASTHMA, ALLERGIC BRONCHITIS AND ASTHMATIC BRONCHITIS)

The tissue changes observed in bronchial allergic disease are identical with the tissue responses encountered in the immediate type of allergic reaction induced by such antigens as pollens, foods and epidermal factors. *Edema, smooth muscle spasm and stimulation of glands* characterize these changes. It is important to note that only the conducting portion of the lungs or the bronchial tree is affected by these tissue reactions, a fact which accounts for the signs and symptoms of bronchial allergic disease.[1, 17] The parenchyma is not involved in the primary allergic tissue response. Any involvement of the parenchyma is secondary. The signs and symptoms of such involvement will be indicated later in the discussion.

Edema involves both peribronchial and mucosal (endobronchial) tissues. Edema of the peribronchial tissues produces rigidity of the bronchial tree, which interferes with the normal expansile and con-

tractile movements of these structures. This tissue involvement, which contributes in a great measure to the respiratory distress of bronchial allergic disease, especially bronchial asthma, is not fully appreciated by most clinicians, with the result that emphasis is usually placed upon the edema of the mucosa which encroaches upon the lumens of the bronchi as the chief tissue involvement in edema.

Smooth muscle spasm producing bronchospasm is a commonly recognized and important tissue reaction in bronchial allergic disease. The distribution of smooth muscle increases as one passes from the bronchi of larger caliber to those of finer caliber, until at the terminus of the respiratory bronchiole a sphincter of smooth muscle guards its entrance into the alveolus. Spasm of the muscle network and the sphincter interferes with the normal ingress and egress of air, an interference which contributes to the dyspnea and also results in air trapping and emphysema.

Stimulation of glands results in increased production of mucus. Mucous glands are more liberally distributed in the larger air passages and decrease in number as the caliber of the bronchial tube decreases until finally, in the smaller bronchioles, no mucous glands are found. It is important to bear in mind that all mucus is produced in the larger bronchi and bronchioles, so that any mucous plugs causing obstruction of the smaller airways must originate from above and be forced down.

The three factors, edema, muscle spasm and glandular secretion of mucus, combine to produce obstruction of varying degrees. Obstruction is the chief factor in the production of signs and symptoms in bronchial allergic diseases. The severity of the clinical pattern depends upon the degree of reaction, and in some measure the clinical pattern depends upon the dominance of either edema, bronchospasm or the production of mucus in the tissue reactions.

Bronchial asthma and those conditions frequently termed "allergic bronchitis" and "asthmatic bronchitis" are fundamentally variations of allergic disease of the bronchi produced by such allergens as pollens, epidermals and foods.

The term "asthma" in the dictionary interpretation means labored respiration. So actually, in the literal sense, one should apply the term "bronchial asthma" to all allergic bronchial disease associated with any degree of impaired breathing. Through usage, however, the term "bronchial asthma" has become identified with a specific clinical pattern characterized by paroxysmal attacks of severe dyspnea with expiratory wheezing. The severe dyspneic state in which the patient brings into action the secondary muscles of respiration—inability to expire air and the diffusely scattered wheezing with the response in most instances, even if only temporary, to epinephrine—is well known to every clinician and recognized as an allergic manifestation. But those

clinical pictures frequently labeled "allergic bronchitis" and "asthmatic bronchitis" are not recognized as variations of allergic bronchial disease related etiologically and pathologically to classic bronchial asthma.

The terms "allergic bronchitis" and "asthmatic bronchitis" have been applied interchangeably to conditions of those children offering a history of frequent "colds" with recurrent or persistent cough accompanied with the lung findings of rhonchi, coarse rales and usually a variable degree of wheezing, but only slight or no respiratory embarrassment. It is important to emphasize that in these children wheezing and dyspnea which dominate the picture of bronchial asthma may be entirely absent, or present in a mild degree. Coarse rhonchi which shift and change their characteristics and position with each cough and each breath dominate the physical findings, while harrassing cough is the chief clinical feature. Apparently the main tissue reaction in these cases is the stimulation of mucous glands resulting in an increased quantity of mucus through which the air passes to produce rhonchi. Peribronchial edema, edema of the mucosa and muscle spasm, all of which produce varying degrees of obstruction and of dyspnea and wheezing, must be either absent or present in only a moderate degree, since in these cases dyspnea and wheezing are either absent or only present to a moderate degree. Dyspnea and wheezing are not the dominant features of this pattern as in bronchial asthma.

The temperature in all variations of uncomplicated bronchial allergic disease, including bronchial asthma, is normal or moderately elevated except in those instances in which the condition is ushered in by an acute upper respiratory tract infection, when there may be an elevation, often as high as 100° to 104° F.

As has been pointed out, so-called allergic bronchitis and asthmatic bronchitis are merely variations of bronchial allergic disease. The term "bronchitis," which means inflammation of the bronchi, implies that infection plays a causative role in the tissue changes. It would be advisable to delete from the literature the terms "allergic bronchitis" and "asthmatic bronchitis" and substitute the name "bronchial allergic disease," which more accurately connotes the causative factors, the mechanisms involved and the tissue changes responsible for the signs and symptoms.

THE ROLE OF INFECTION IN BRONCHIAL ALLERGIC DISEASE

As has been indicated, when bacteria or bacterial products serve as antigens, they evoke a delayed type of skin reaction. When vaccines, either stock or autogenous, are used for skin testing, a delayed skin response similar to the tuberculin reaction is observed when sensitivity is present. On the basis of the delayed type of reactivity we cannot explain the reversible tissue changes caused by edema, muscle spasm

and stimulation of glands responsible for the signs and symptoms of uncomplicated bronchial allergic disease. If infection cannot explain these tissue changes, what is the role of infection in allergic bronchial disease? Infection has a dual role in allergy, a *primary* and a *secondary* role.[2, 3]

In its *primary role* bacteria or bacterial products serve as antigens to produce tissue changes associated with the delayed type of allergic response. These changes cannot explain the findings encountered in allergic bronchial disease.

In its *secondary role* infection may serve as "*provocateur*" to influence the course of the existing allergic state without any participation on the part of infection in the underlying allergic tissue changes; or infection may serve to *complicate the tissue responses of allergic bronchial disease* induced by the immediate type of reactivity.

When infection does *influence the course of existing allergy*, it produces a distinct pattern for the allergy. The pattern observed is one of two types, the type being determined by the nature of the infection. The first pattern (Fig. 2) is observed in association with pertussis, measles, chickenpox, mumps, Kaposi's disease, roseola infantum and the epidemic viral diseases. With these diseases, during the prodromal stage or period of invasion, there is an aggravation of the pre-existing allergy. The symptoms during this period will usually be determined by the

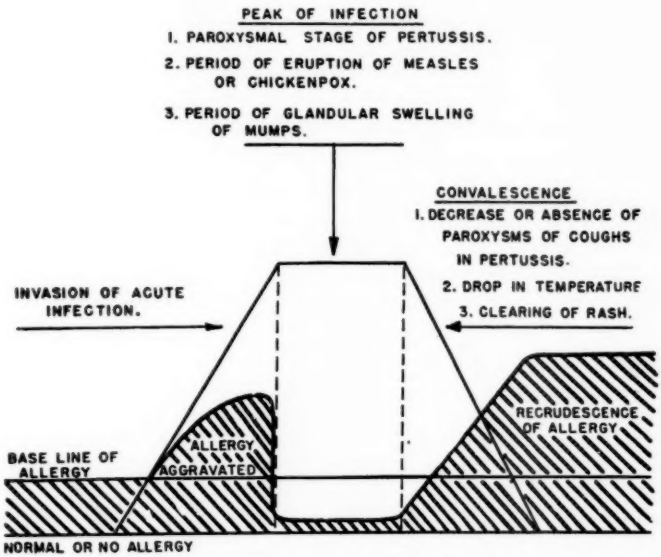
PEAK OF INFECTION
1. PAROXYSMAL STAGE OF PERTUSSIS.
2. PERIOD OF ERUPTION OF MEASLES OR CHICKENPOX.
3. PERIOD OF GLANDULAR SWELLING OF MUMPS.
CONVALESCENCE
1. DECREASE OR ABSENCE OF PAROXYSMS OF COUGHS IN PERTUSSIS.
2. DROP IN TEMPERATURE
3. CLEARING OF RASH.
INVASION OF ACUTE INFECTION.
RECRUDESCENCE OF ALLERGY
ALLERGY AGGRAVATED
BASE LINE OF ALLERGY
NORMAL OR NO ALLERGY

Fig. 2. Illustrating pattern of allergy in association with pertussis, measles, chickenpox, mumps, Kaposi's disease, roseola infantum and epidemic viral diseases.

patient's previous complaint, so that the asthmatic child will suffer with asthma or bronchial allergic disease; and the eczematous child will present an aggravation of his eczema. As these acute infectious processes approach their full development, the symptoms of allergy become less severe, so that at the fastigium of the disease the child will be free of symptoms of allergy.[10, 16] The nose will be clear; the lungs will be clear; the skin will be clear. Actually, at the peak of these infections the level of allergy is less than before the invasion of the acute infectious process. This period corresponds to the paroxysmal stage of pertussis, the exanthem of measles, the eruption of chickenpox, the vesiculation of Kaposi's disease, and the fever of epidemic viral diseases. With convalescence there is recrudescence of the allergy, or the allergy may recur, and when it does recur, it may appear with greater severity and greater intensity than before the onset of the acute infectious process. A new base line for the allergy is established, so that the child with mild symptoms of allergic rhinitis may complain constantly of nasal distress; the asthmatic child may have persistent pulmonary findings, or in some instances experience his first attack of asthma; the eczematous child will show an aggravation of his rash.

There are many practical clinical applications to be drawn from this pattern. A patient incubating an acute infectious disease, such as measles, mumps, chickenpox or pertussis, may suffer with the symptoms of bronchial allergic disease, or even bronchial asthma, which fail to respond to all therapeutic measures. Only after the disease has fully developed do the allergic signs and symptoms resolve. This is important to bear in mind in refractory cases of allergic bronchial disease offering a history of exposure to an acute infectious process.

The chest findings of bronchial allergic disease, including bronchial asthma, clear with the paroxysmal stage of pertussis. A patient presenting the physical findings of bronchial allergic disease and bronchial asthma which clear while the cough becomes progressively aggravated should lead one to consider a diagnosis of pertussis. The typical blood picture and the paroxysmal characteristic of the cough with the absence of pulmonary findings will help to confirm such a diagnosis.

The onset of the first attack of asthma following an acute infectious illness as measles, chickenpox, mumps and especially pertussis is well recorded in the literature. In a similar manner other forms of bronchial allergic disease (allergic bronchitis and asthmatic bronchitis) may be ushered in by an acute infectious process. In such patients the allergic state has been present from birth, but perhaps not manifested clinically, or only in a mild form. The acute infectious process disturbs the balance or the threshold, whichever the mechanism may be, so that a previously mild allergic state becomes troublesome with distressing symptoms of bronchial allergic disease. It is like a smoldering volcano which becomes violently active.

The second pattern (Fig. 3) is observed most commonly in association with acute infection of the upper respiratory tract with neutrophilic leukocytosis, such as rhinopharyngitis, acute tonsillitis with or without adenitis, adenoiditis, sinusitis, acute otitis, or any combination of involvement of the upper respiratory tract. With these infections there is no apparent change in the degree of the allergy during the period of invasion, but at the height of the infection there is an aggravation of the allergy. Corresponding to the peak of the infection, the allergy is most severe. The child with allergic rhinitis will have severe nasal symptoms, the asthmatic child will suffer with severe asthma or allergic bronchitis, while the rash of eczema will be aggravated, or itching is frequently more intense.

This is the commonly encountered pattern of acute upper respiratory tract infection which precipitates bronchial allergic disease. The child may suffer with an acute pharyngitis, tonsillitis or at times even otitis media. Cervical adenopathy may be present. The temperature may range from a slight elevation to 104° or 105° F. The symptoms are those of malaise, sore throat and cough followed in rapid sequence by lower respiratory tract signs and symptoms. When bronchial asthma is precipitated, respirations are labored, the accessory muscles are frequently brought into action, and general wheezing is audible. In nonparoxysmal bronchial allergic disease cough and diffusely scattered rhonchi are the respiratory pattern. If treatment with fluids and antibiotics or sulfonamides is instituted early, the entire picture may be dramatically resolved within a few hours.

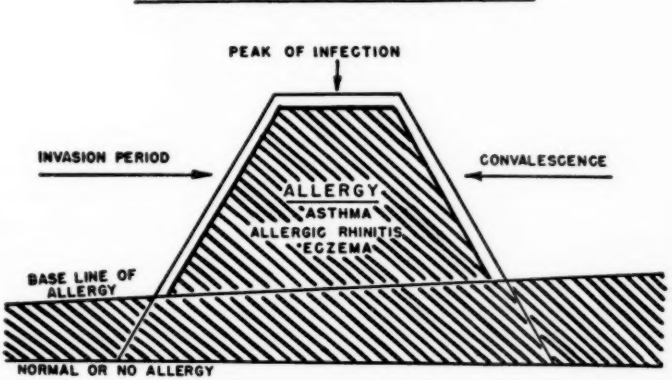

Fig. 3. Illustrating pattern of allergy in association with acute upper respiratory tract infection with neutrophilic leukocytosis, such as rhinopharyngitis, acute tonsillitis with or without adenitis, adenoiditis, sinusitis, acute otitis or any combination of involvement of the upper respiratory tract.

This clinical pattern of infection, when constituted of recurrent episodes of upper respiratory tract infection with bronchial allergic diseases, frequently raises the question of the advisability of tonsillectomy as a preventive measure against the pulmonary involvement. If the tonsils are infected, they should be removed surgically. If they are not infected, removal will in no way prevent the recurrence of the condition.

These findings represent the role of infection as "provocateur." Infection serves to disturb the balance of the allergic state with the precipitation of respiratory symptoms. The infection in no way participates in the allergic tissue responses.

Infection Complicating the Tissue Responses of Bronchial Allergic Disease

As has been indicated, *edema, smooth muscle spasm* and *stimulation of glands* induced by such common allergens as pollens, environmental factors and foods combine in the involvement of the bronchial tree to produce varying degrees of obstruction responsible for the different patterns of bronchial allergic disease.

When *edema* and *smooth muscle spasm* are the chief components of the tissue response, infection is not a common complicating factor. With edema and smooth muscle spasm, air trapping with resulting emphysema is the sequel of incomplete obstruction. Air is in motion, but there is interference with its egress. With movement of air, infection is not a complicating factor.

When *mucus* is a dominant tissue response, infection plays an important secondary role. With mucus, particularly when it is thick, tenacious and viscid as occurs in dehydration, plugs are formed which block the airways, resulting in collapse of parenchymal tissue and atelectasis. Stagnation and retention of secretions predispose to superinfection, which soon intervenes as a complicating factor.

If a large bronchus is plugged, a large segment or even an entire lobe may become atelectatic. With sudden plugging of a bronchus the onset of symptoms is acute, with severe cough and dyspnea, rapid respiration, and even a high degree of cyanosis. Temperatures may be elevated to 104° to 105° F. The child presents a picture of serious illness. If the plug is dislodged before the onset of infection, there may be a dramatic clearing of symptoms, sometimes as rapid as the onset. This occurs occasionally with dislodging of the plug by coughing, but more frequently after early administration of epinephrine hydrochloride.

With the gradual formation of a plug in a large bronchus, atelectasis may develop unsuspectedly without any sudden aggravation of the clinical picture. Diagnosis is made from the physical findings typical

for atelectasis and from the roentgenograms. Infection commonly complicates this pattern.

Plugging of the smaller airways leads to small patches of atelectasis which are soon complicated by secondary infection producing pneumonitis. With a sudden onset the symptoms are more acute. Fever is present, usually between 101° and 103° F., but occasionally it may rise to 104° or even 105°. Cough is harrassing, respirations are rapid, and dyspnea is severe, with at times involvement of the secondary muscles of respiration. Cyanosis may be pronounced. Examination of the chest reveals diffusely scattered coarse rales with little or no wheezing. At the base of the lungs patches of crepitant rales may at times be heard, but these are not constant findings. When the patches of involvement are small, the findings may be overshadowed by the surrounding aerated lungs, or, when atelectasis is present, there may be an absence of adventitious sounds. Dehydration which results from fluid loss through exaggerated respiration, the failure of the child to take fluids, or from vomiting adds to the acuteness of the picture. Although a leukocytosis is commonly present, this finding is not essential to a diagnosis. The presence of a complicating infection is obvious to the clinician.

With a subacute or more gradual development of mucous plugs, a pattern in the lungs may be produced which is similar to the acute picture, but with a less violent clinical pattern. Cough is the outstanding symptom. Dyspnea may be present, especially on exertion, but is not pronounced or distressing. Fever may be absent or only slightly elevated to 100° or 101° F. orally. Examination of the lungs reveals diffusely scattered rhonchi with little or no wheezing. At times even rales, suggestive of small pneumonic patches, may be heard, but not demonstrable by roentgenogram. The auscultatory pattern is not a constant one. There is shifting and changing with each cough and each respiration. Infection is a common complicating factor which in most cases can be confirmed by an elevated white blood cell count with a predominance of polymorphonuclear forms in the differential picture.

At times infection seems to smolder without the production of acute symptoms. Dyspnea is absent or mild, temperature may be normal or slightly elevated, but cough is persistent and usually the determining symptom for bringing the child to the physician. On physical examination the only finding is that of diffusely scattered coarse rhonchi. Such a pattern may persist for weeks or even months without response to the usual therapeutic measures for bronchial allergy. With specific therapy directed against the infection an immediate response is frequently observed.

The failure of these patterns to respond to allergy management and their frequently dramatic responses to specific therapy for infection lead many clinicians to the erroneous conclusion that they are dealing

with an allergic response to bacteria or bacterial products. The allergic tissue changes in these conditions are characterized by edema, smooth muscle spasm and stimulation of glands, induced by such common allergens as pollens, environmental factors and foods. The tissue changes produced by the superimposed component of infection are the same as the inflammatory tissue reactions observed in pulmonary infection without an allergic component. Definitive control of the allergy through the usual measures will prevent the allergic tissue response and avoid the complicating factor of infection.

The reversible tissue reactions induced by such common allergens as pollens, epidermal factors and foods involve only the conducting portion of the lungs or the bronchial tree. Parenchymal involvement in such cases is a complication of the obstructive features of these reactions. Primary allergic parenchymal involvement is usually associated with the delayed type of allergic response induced by bacteria and bacterial products. This pattern is encountered in chronic Loeffler's syndrome and the pulmonary involvement associated with rheumatic disease, allergic vasculitis and so-called collagen diseases. Primary allergic involvement of the lung parenchyma occurs in childhood at all ages, but is less frequent than in the adult.

It is likely that the cases of so-called *intrinsic asthma* may fall into the category of primary allergic parenchymal involvement. Clinically, these patients may suffer with dyspnea and wheezing, but since the involvement is parenchymal and not bronchial, the term "asthma" should be applied and not "bronchial asthma." These patients show no response to skin tests with the ordinary allergens such as pollens, environmental factors and foods. They also fail to show response to the usual measures of treatment for bronchial allergic disease. These cases should not be confused with (1) those instances in which primary parenchymal involvement may be superimposed upon a bronchial allergic response, or (2) those cases in which nonallergic parenchymal involvement complicates primary bronchial allergic disease. In both instances skin testing may be positive with pollens, environmental factors or foods, but there is no response to treatment with the usual measures for allergic disease.

TREATMENT

The management of bronchial allergic disease with infection must take into consideration the two basic factors concerned. First, the underlying tissue changes induced by the allergic reaction must be controlled, and, second, either the contributing or complicating infection must be combated. Symptomatic treatment of the allergic reaction is concerned with relieving the obstruction produced by the edema, muscle spasm and increased production of mucus.[4]

Sympathomimetic Drugs

For the control of edema and muscle spasm the sympathomimetic drugs—epinephrine hydrochloride, 1:1000, ephedrine and Propadrine—are most effective. Of these drugs, epinephrine hydrochloride, 1:1000, administered hypodermically, is the most efficient. However, because its action is of such short duration, epinephrine is only useful to combat acute episodes of bronchial asthma. Epinephrine hydrochloride, 1:100, as a spray is not recommended. Although it may effect temporary relief from acute symptoms, the risk of deleterious action upon the mucosa and the cultivation of the "spray habit" outweigh any benefits derived from this form of administration.

Ephedrine and phenylpropanolamine (Propadrine) are used to prevent the occurrence of acute episodes and to treat mild attacks of allergic bronchial disease. Ephedrine, through stimulation of the higher centers, may produce the unpleasant side effects of jitteriness, nervousness and wakefulness. These can be counteracted by combining the drug with small doses of phenobarbital. The barbiturates, because of their depressing action on the respiratory center, should not be used alone.

Propadrine usually does not stimulate the higher centers. When ephedrine is not tolerated, Propadrine may be substituted.

The xanthine drugs, theophylline and aminophylline, are effective chiefly through their bronchodilator action. In therapeutic doses their vasoconstrictor action is not prominent. In children, theophylline and aminophylline not infrequently produce gastric hemorrhage, even after parenteral administration. Shocklike reactions and fatalities have been reported to follow administration of these drugs. These undesirable side reactions have occurred after administration of a single suppository containing either aminophylline or theophylline. Because of the risk of these reactions, the xanthine drugs are not recommended for the treatment of bronchial allergic disease in children.

Antihistaminic Drugs

The antihistaminic drugs are not effective in the treatment of bronchial allergy. Because of their atropine-like drying action, they may predispose to complications resulting from plugging from dried secretions.

Control of Mucus

For the control of mucus, the most effective expectorant is water. The development of dehydration which results from fluid loss through exaggerated respiration, from failure of the child to take fluids or from

vomiting is a common tendency in bronchial allergic disease. Administration of large quantities of fluids is the best safeguard against inspissation of secretions with subsequent plugging. When fluids cannot be taken orally, parenteral administration must be considered. When parenteral fluids are administered, only plain water with 5 per cent dextrose should be used. Saline solution aggravates the edema. Not infrequently, in spite of what is seemingly an adequate fluid intake by mouth, parenteral fluids are necessary for control of symptoms.

Potassium iodide in saturated solution is the expectorant drug of choice. Through its action secretions are liquefied and their elimination facilitated. Syrup of hydriodic acid, although frequently recommended, is much less effective than saturated solution of potassium iodide.

Treatment of Cough

Cough is undoubtedly a reflex effort to eliminate the factors producing obstruction. All sedative cough mixtures, especially those containing opiates in any form, are contraindicated. By suppressing the cough they promote a retention of secretions which results in plugging with ensuing undesirable complications. Relief of cough should be effected through correction of obstruction by the use of sympathomimetic drugs, hydration and simple expectorants such as potassium iodide. Frequently a warm moist atmosphere will help relieve coughing.

Oxygen

In uncomplicated bronchial allergic disease there is no hypoxia. Administration of oxygen is not indicated. Use of the various appliances for the administration of oxygen will frequently cause a degree of anxiety and apprehension in the patient. Unless a complication such as severe cyanosis is present, oxygen is not recommended for the treatment of bronchial allergic disease.

Steroids

The use of steroids is discussed elsewhere in this symposium (p. 745).

Control of Allergic State

Definitive treatment of allergic bronchial disease consists in controlling the underlying allergic state through the elimination of offending environmental factors when possible, the elimination of offending food factors when identified and through hyposensitization. Successful control of the allergic tissue reactions will prevent the occurrence of fre-

quently recurring infections which aggravate and complicate bronchial allergic disease. The clinician will soon recognize that in bronchial allergic disease with infection the underlying immune mechanism operates in two directions: namely, the allergic reaction predisposes to infection, while infection aggravates the underlying allergic state. By controlling the underlying allergic reaction the likelihood of infection is prevented, or if infection is experienced by the child, the clinical pattern is not complicated by the symptoms resulting from associated allergic tissue reactions.

Accepting the thesis that bacteria and bacterial products do not explain the tissue reactions observed in bronchial allergic disease, we do not recommend the use of either stock or autogenous vaccines in the treatment of allergic bronchial disease, either with or without a component of infection. In view of the tissue reactions induced by bacterial antigens, we feel there is an element of hazard in their use.

SUMMARY

The tissue reactions of uncomplicated bronchial allergic disease (bronchial asthma, "allergic bronchitis" and "asthmatic bronchitis") are caused by the reversible tissue responses associated with the immediate type of immunologic reactivity. Pollens, environmental factors and foods are the chief antigens concerned with the immediate type of reactivity. Infection, which produces a delayed type of immunologic reaction, does not explain these tissue responses. Infection plays a secondary role in bronchial allergic disease. First, it may act as "provocateur" to influence the course of the existing allergic state without any participation on the part of infection in the underlying tissue changes; or, second, infection may serve to complicate the tissue responses of allergic bronchial disease induced by the immediate type of reactivity.

Treatment of bronchial allergic disease with infection must take into consideration the underlying tissue changes induced by the allergic reaction and the contributory or complicating infection.

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THE PROGNOSIS OF ASTHMA IN CHILDREN

FRANCIS M. RACKEMANN, M.D.

In the *New England Journal of Medicine* for May, 1952, Mary C. Edwards and I[1] presented the results of a follow-up study of 688 patients whose asthma began in childhood. Most of that report was concerned with the 449 children who had been seen first before the age of 13. The group was not selected—all the asthmatic children were included—and we believe that our figures show the true outcome of asthma in children. Each of these children was followed up for at least 20 years, and we were pleased to receive follow-up notes from all but 29 of them.

In this group of cases, boys outnumbered girls about two to one. In our study the patients were divided into groups in accordance with the exciting cause of their symptoms, and this statement requires comments.

First, the cause of asthma is not usually clear-cut and single. On the contrary, mixed causes are the rule. The patient may be sensitive to dogs, cats, feathers or pollens, both by skin test and by his clinical experience, and in many cases the relation between symptoms and exciting cause is clear enough. In other cases, however, the symptoms develop only when some other factor comes to complicate the primary allergy. New colds will increase the degree of sensitiveness, and then simple fatigue, or psychogenic factors such as fear and frustration—the inability to keep up with playmates—will increase the effect of sensitiveness and make a slight exposure effective. Multiple causes must always be considered; they are almost the rule.

Secondly, positive skin tests do not always point to the cause of trouble. All too often one reads about asthma due to either foods or dusts and finds that the diagnosis was based simply on the finding of positive skin tests and was not supported by the clinical tests of elimi-

nation or of deliberate controlled exposure. It is well known that reactions of the skin may be quite different from reactions of the membranes or of the body as a whole. Occasionally one finds that the positive skin tests found in children represent a potential sensitiveness which develops later into a true clinical reaction.

In older patients the skin tests may reflect the past history rather than the present illness or the potential future. The history may show that, in childhood, exposure to dogs or cats would cause asthma, or perhaps the asthma had a seasonal relation which could be correlated with the finding of positive skin tests to pollens, the point being that both in children and in adults there are many cases in which positive skin tests have no symptoms to go with them. In each case the clinical significance of the skin tests must be checked with the history or with changes in environment or diet which will show whether or not the skin-test finding makes sense.

All this means that diagnosis is always difficult, and that is the reason why the classification of causes, hoping to derive figures for the incidence of the different groups, is unsatisfactory. Our figures can be only approximate.

Our study of 449 cases showed that in about 25 per cent the asthma was due to animals, in 8 per cent to foods, and in 5 per cent to pollens. In the largest group (43 per cent) the cause was "mixed and unidentified" so far as sometimes one, sometimes another factor could be shown to precipitate the new attack. Finally, there was a group whose skin tests were entirely negative (18 per cent).

Taking these groups together, we found, 20 years later, that 30 per cent were "cured" in the clinical sense. No longer did they have any trouble when exposed to animals or pollens, and they were able to eat all foods, including the eggs, wheat, milk, fish or nuts which had caused trouble in childhood.

In addition to the "cured" group there was another 20 per cent who no longer had asthma to any troublesome extent, but they knew that they were still clinically sensitive to the dusts, or perhaps the foods, which had caused asthma before. They were doing well because they had learned the importance of avoiding all contact with animals; they had learned to control their hay fever, either through specific treatment or by proper use of antihistaminic drugs; and they could lead a normal life in perfect comfort even if they still had to watch their step.

We could say, then, that 30 per cent plus 20 per cent, or 50 per cent, of these 449 patients were essentially and clinically well.

When did they become well? At what age did the asthma clear? When do these children "outgrow" their sensitiveness? Mrs. Edwards and I tried to answer these questions. Whereas the average age of "cure" was 14.7 years, there were wide variations. In one or two cases

the asthma stopped abruptly as soon as a cat was sent away, and the child had no further trouble after that important day.

I can recall a small boy, son of anxious parents, whose asthma was bad. One Sunday I drove out to his home in the country and astonished his mother when I removed 7 pillows, stuffed with badly broken down kapok, from the sofa and chairs in the parlor and drove off with these old, dusty kapok pillows in the back of my car. I learned later that I had taken the boy's asthma away with the pillows, and in the 20 odd years since then this boy has never had asthma again.

House visits like this can be very productive at times.

In other cases the "cure" was delayed. The diagnosis was not so clear-cut, and neither the doctor nor the family was convinced that the exciting cause was a source of dust at home. For example:

Another boy with a number of positive skin tests to foods, as well as dusts, was treated with diets and also with injections of dog hair extract. He was better, but he was not "cured." Some time later I met his mother: "How is Willie?"
"He is all well, thank you: he has had no trouble since last summer."
"What about the dog?"
"Oh, dear, what a tragedy! Rover was run over by a truck!"
"When was that?"
"In the middle of last July some time."

The real tragedy is that neither this doctor nor the family had the courage to make those simple experiments which would have proved or disproved the idea that the dog was responsible. Either the dog could have been sent back to the kennels and the house thoroughly cleaned of dog hair, or the boy could have been sent to live with "his uncle" or "his grandmother." Since one could be quite sure that in the clean environment of any hospital this boy would become clear of asthma in about four days, the answer to the experiment should appear promptly, depending upon the thoroughness of the cleaning process. To allow two weeks should be enough.

There is another group of children who have done well so far as asthma is concerned. In 21 per cent of the series the original asthma has subsided, but sensitiveness of another kind has developed—the patients, now in their late teens or early twenties, have developed hay fever. The capacity to develop sensitiveness still shows itself. In most cases it is pollens which cause this later difficulty. Incidentally, this observation tells us something about the nature of the different allergenic substances. The specific substances in animal danders, foods, and perhaps in some domestic dusts, are proteins, presumably. Exposure of the patient can give rise to allergy, but, as our figures show, this allergy passes off in the course of time, presumably because the protein substances finally lead to a real immunity. These proteins are fairly effective as allergens, but they are also good antigens. Pollens, on the other hand, are excellent allergens, but very poor antigens, and so it is always difficult to demonstrate antibodies to pollens in the patient's blood. It

is clinical observations such as this that can throw a little light on the chemistry of our problem.

"Asthmatic bronchitis" is a convenient description of a rather large group of cases. Here are children and young adults with a story of wheezy colds coming two, three or four times each winter. Each attack begins with a new cold and leads to a wheeze which lasts for 2 to 7, or even 10, days, and then, when the attack passes, the patient is perfectly clear until the next time.

There are two groups of these cases. In some there is evidence of a sensitiveness to some dust or food substance which by itself causes no trouble, but which can be set off by the new infectious process. The bronchitis has excited the asthmatic tendency.

In the second group the infection appears to be sufficient by itself to explain the attacks, and here the diagnosis probably is "bacterial allergy," even though so far it is difficult to prove a hypersensitiveness to the specific organism or the products of its growth.

In all these cases of asthmatic bronchitis the prognosis is good, and most of the patients outgrow their trouble in their late teens, when the resistance to new infections increases. The prognosis is better when skin tests are negative and one can show that the infection by itself is enough to explain the trouble.

Eczema sometimes precedes asthma in children. In our classification, foods caused asthma in 36 patients, or 8.1 per cent. Each of these 36 patients had had eczema either in infancy or shortly before the onset of asthma—say, between the ages of 7 and 10. The skin tests suggested that the eczema was due largely to foods, and this relation was demonstrated in most of the cases.

Atopic eczema has a typical distribution, with lesions in the bends of elbows and knees—the cubital and popliteal spaces—and on the face and neck. It is this distribution which makes the diagnosis. In most cases this early eczema clears soon after the asthma has begun, but there are a few patients whose childhood eczema persists into adult life, and each of these presents a difficult problem. Elimination of foods and dusts of all kinds, and attempts at desensitization, have not accomplished much for these unfortunate people. For some of the older patients cortisone has been a godsend. Whether the presence of eczema can modify the prognosis of asthma in children is not yet clear. The impression so far is that the presence of eczema is not a good sign. On the other hand, our survey includes a number of patients who have recovered entirely from both their eczema and their asthma.

Lesions of the nose and throat require a word. In adults, polypoid pansinusitis is a part of the disease: It is not a cause of the trouble, and that is the reason why operations on the nose have not benefited our patients. In children, lesions of the nose and sinus are unusual, and one does not see this complication in them.

Deformities of the chest cage, with pigeon breast, barrel shape, and kyphos, are seen at times. Whereas in older people these deformities carry a bad prognosis, in children it is gratifying to see that in the course of time the deformity tends to correct itself, and the patient often comes out all right, although he has to be cared for carefully for a considerable time.

Mrs. Edwards' and my report showed that 30 per cent of our patients were virtually "cured," another 20 per cent have no trouble so long as they avoid the offending cause, and another 21 per cent no longer have asthma, but do have hay fever. This makes 71 per cent who have done well. What about the remaining 29 per cent? At the end of 20 years 15 per cent still had mild symptoms, but only 11 per cent of the total were having any real trouble, and in only 2 of this 11 per cent were the symptoms bad enough to require treatment in a hospital.

Eleven patients, or 2.4 per cent of the total series, have died from various causes. Four died, presumably, of asthma—at least the description of the last illness as given in the follow-up letter was compatible with that diagnosis. So far a study of their records does not reveal any factor in the history or examinations which would have pointed to the dreadful outcome, but the point is important, and we are working on it.

In conclusion, one can say that the prognosis of asthma in children is good. Seventy per cent are virtually symptom-free, and in another 15 per cent the symptoms remaining after age 20 are mild. It is only in 11 per cent of the total that the asthma continues to be troublesome, and in only 2 of the 11 per cent has it been severe. Less than one out of every hundred (0.88 per cent) children with asthma has died of that asthma, but our study of the four cases is not yet complete. The mechanism of asthma includes the capacity to develop sensitiveness, and so it is that these patients are prone to develop hay fever in later life. The sequence of eczema in infancy, asthma in childhood, and hay fever later on, is typical, even though it is not often a threat to the general welfare and happiness of the patient.

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GENERAL MANAGEMENT OF THE ASTHMATIC CHILD

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One of the first considerations in dealing with the problem of childhood asthma is to be sure the parents of the child have a correct basic understanding of the nature of allergic disease. They should know that sensitization is not spontaneous, but comes about only through exposure; that it is possible for new sensitivities to develop and for previous sensitivities to disappear. They should be told of some of the limitations of skin testing before, not after, the skin tests are done. Certain other concepts have proved useful, which I find of value in assisting the parents to understand their child's problem. These same concepts have also been of help to me in managing asthma as a disease, and are as follows: (1) the idea of allergic equilibrium and of the asthma "trigger" mechanism, (2) the value of continuity symptoms of allergic rhinitis in treating asthma, (3) the importance of environmental control in the house dust-sensitive patient.

PARENTAL ORIENTATION

Orientation along these lines can be given to a parent in a printed pamphlet. The following is slightly altered from the one used at the University of California Pediatric Allergy Clinic for this purpose. The mother usually reads this while skin tests are being done and then takes it home to discuss with her husband.

SOME COMMENTS ON ALLERGY FOR PARENTS

Allergy may be defined as an abnormal reaction in some portion of the body to substances from the outside environment. Such substances may be taken into the

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body through the nose and lungs (pollens, house dust, animal danders, etc.), by mouth (foods, beverages) or through the skin (by contact with woolen clothing, animals, rugs, insect bites, etc.). An allergic person is said to be *sensitive* to various substances. The substances themselves are called *allergens*, and may produce symptoms in a person who is sensitive to them, though they do not cause trouble in a normal person.

The most common symptoms produced by allergy are hay fever, asthma, eczema and chronic "stuffy nose" (allergic rhinitis). An allergic person may have only one of these symptoms, such as hay fever, or he may suffer from one symptom at one period of life and a different symptom at a later period. A frequent sequence is for an infant to have eczema which clears up early in childhood and then have allergy of the nose or asthma later in childhood.

The *tendency* to become sensitized or allergic to some otherwise harmless substance is usually inherited. It is a peculiarity of the constitution which persists throughout life, just as the coloring of the eyes is an inherited characteristic which also persists.

What one becomes sensitive *to* depends, in part, to *what* one is exposed, as well as the *amount* of such exposure. Thus a person who has inherited this tendency may become sensitive to cow's milk shortly after birth, or to dog hair at the age of six years after acquiring a dog. Throughout his life he may have new sensitivities as he undergoes new exposures. The previous sensitivities may remain, or may gradually be lost. What produces sensitivity depends also upon whether or not a substance is a good "sensitizer." Some pollens, such as pine pollen, despite their abundance, seem never to cause allergy. Other substances, such as grass pollen, house dust, feathers and chocolate, have shown themselves to be relatively good "sensitizers."

There are two fundamental ways of treating allergy: (1) removal of the causes of the allergy; (2) an attempt to build up the patient's resistance to these causes by injection of increasing amounts of allergens at regular intervals. Strictly speaking, allergy is not "cured," but only kept under control so that it does not produce symptoms.

Removal of allergens is preferred if it can be carried out in a practical manner. Obviously, if all the allergens could be completely prevented from entering the body of the allergic subject, the symptoms would cease. This ideal is attempted in many ways: if the allergen is an animal hair, the offending animal is removed; if it is a food, it is eliminated from the diet; if it is house dust, sources of such dust are eliminated from the bedroom and reduced as much as is possible in the other rooms.

In such cases the amount of relief from symptoms which is obtained is in direct proportion to the thoroughness with which the allergens are removed.

The second method of treatment, i.e., immunization by injections of small amounts of allergens, is not as regularly beneficial as the first method, but in some situations is the only method which can be used. For instance, if the allergens are pollen from certain grasses, trees or weeds and the sensitive person cannot move to a different locality where such grasses, trees or weeds do not grow, he cannot very well avoid the pollen which is everywhere suspended in the air. Pollen is carried by the wind for miles, so that removing the vegetation around the house does not solve the problem. Injection treatment becomes the only recourse. In other situations, if elimination of allergens has been carried out as completely as possible, and improvement has occurred, *further* improvement—if necessary—may come from graded injections. House dust extracts are sometimes used in this way, but *only* after as complete a removal of house dust as is possible. Immunizing injections do not help in food allergy and are not used.

Some very sensitive persons must avoid allergens absolutely and completely, but most allergic patients can stand mild or moderate contact with their allergens. Occasionally patients state that they used to have hay fever (or eczema or asthma), but do not have it any longer. There are three possible explanations for this:

1. The patient may have moved to a locality where the pollen which was responsible for his symptoms does not exist.

2. He may have lost his sensitization—people are not necessarily sensitized permanently, although they always maintain the *capacity to be sensitized*. One may lose or "outgrow" a sensitization, and may pick up new sensitizations while doing so.

3. He may still be sensitive, and yet be able to tolerate larger doses than formerly, owing either to spontaneous improvement or to improvement brought on by injections.

Allergic persons who can tolerate some exposure to their allergens, without developing symptoms, are considered to be in allergic equilibrium or allergic balance; i.e., the amount of allergens taken in is balanced by the individual's "tolerance" or "resistance."

Nonallergic factors may place an additional burden on the patient and thus disturb allergic equilibrium. Respiratory infections, such as common colds, may increase the total load to a point beyond a patient's tolerance and thus upset what was previously a balanced allergic state. Fatigue, emotional tensions, excitement, exertion, cold foggy weather and many other factors may also increase the burden, upset the balance, and allow an allergic attack to develop.

For instance, an asthmatic person may be sensitive to many allergens such as house dust, horse dander, grass pollen and others. For months he may have almost no symptoms even though he is breathing a certain amount of house dust into his body during his daily activities. In this situation he is considered to be in balance. However, let him one day sweep the floors, and the amount of house dust which he inhales may be so increased that his allergic balance is severely upset and asthma results. Or, if he comes in close contact with a horse or drives in the country when grasses are pollenating, the additional load of these allergens may upset his balance. In these instances an excessive intake of allergen is responsible for causing asthma. On the other hand, the allergic balance may be disturbed without the intake of additional allergens beyond the usual amount. Such may be the case if a "cold" develops, or if there is emotional tension or excessive fatigue, or some other occurrence which, added to the usual intake of house dust, is enough to tip the balance.

Another way to think about this is to consider the problem as a loaded gun. The nose or throat infection, emotional tension, chilling or excessive fatigue can be regarded as something which pulls the trigger and thereby sets off the explosion (i.e., the asthmatic attack); the bullets are the allergens (house dust, pollens, animal hairs, etc.). The most effective way to prevent an explosion is to discover and remove the bullets.

The first step, then, in treating allergy is to detect which substances, or allergens, are the bullets in the analogy. This is done in several ways. One most important method is close observation over a long period of time as to what contacts, situations or foods precede the development of symptoms. *This depends upon the alert and accurate observations of the parents.*

Another way in which the allergens may be detected is through skin tests. There are several methods of skin testing, the most common being the scratch test. Positive tests are only *clues* to allergens and must be interpreted cautiously, since they are not all equally reliable. *Food tests, especially,* are less reliable than tests to air-borne substances (inhalants). Negative tests do not always prove a substance harmless; the final answer depends on therapeutic trial.

A third method of detecting offending substances is to eliminate systematically certain *suspected* allergens for a trial period of several weeks. Although this is a long and detailed procedure, it sometimes produces definite improvement in symptoms and may thus indicate which allergens are responsible.

Finally, observation of the course of the patient's nasal symptoms can often prove helpful. What causes the patient to cough and wheeze (asthma) will often cause him to sneeze and rub an itching nose (allergic rhinitis) as well. The nose symptoms are likely to occur daily, while the asthma may be intermittent. The parent's observation of what causes the child to sneeze and rub his nose will often prove valuable clues to the cause of his asthma. Improvement in these symptoms of nasal allergy often indicates that improvement can be expected in the asthma as well.

Many parents ask, "Will my child outgrow asthma?"

Although asthma may spontaneously improve at *any* time and especially at puberty, it may also worsen at any time or simply not change, even at puberty. Waiting, possibly years, to see whether spontaneous improvement will occur—meanwhile trying to get along with drugs rather than determining the cause of asthma—is not likely to prove satisfactory to the parent or helpful to the child.

Even when no asthma is present, treatment of a patient with hay fever or chronic allergic nose symptoms will often do much to improve his general health and may prevent asthma from developing in the future.

ALLERGIC EQUILIBRIUM

The concept of allergic balance or equilibrium is a most useful one for both parent and physician to have, and is best diagrammed in the manner set forth by Dr. Samuel Feinberg in one of his early publications and reproduced here with modifications (Fig. 4). Four basic figures of a scale are involved, one in balance and three out of balance.

The first (Fig. 4, *A*) represents the condition of an asthmatic patient who is in allergic equilibrium. His inherited constitutional make-up has permitted him to become sensitized, but the sum total of his exposure to the allergens to which he is sensitive is within his tolerance, and he does not wheeze. Either of two things may happen to induce an attack. He may experience a greater exposure to specific allergens and thus upset his allergic equilibrium (Fig. 4, *B*), or nonspecific precipitating factors may be added to his allergic load. Through them his allergic equilibrium may be tipped into an asthmatic attack (Fig. 4, *C*). These nonspecific factors may be such things as odors (paint, perfume), chemical or mechanical irritants (smog, smoke, chalk dust, and so on), climatic factors, upper respiratory tract infections, exertion and fatigue, and emotional disturbances. By themselves, without the underlying allergy, they would not cause asthma.

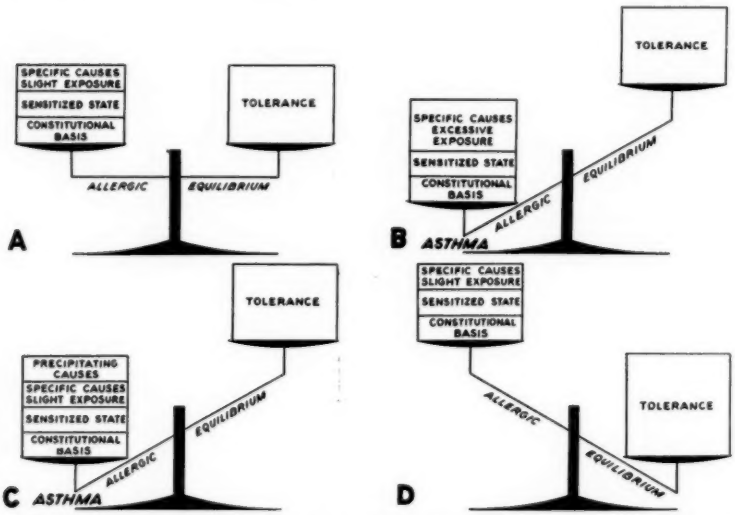

Fig. 4. Allergic equilibrium may be upset by excessive exposure (*B*) to otherwise tolerated allergens (*A*). Allergic equilibrium may be upset also by nonallergic "precipitating" causes added to otherwise tolerated specific antigens (*C*). The greatest margin of safety is provided if tolerance can be increased by injection therapy and exposure held to a minimum (*D*). (Modified from Feinberg: *Allergy in General Practice*. Lea & Febiger.)

A final possibility is an alteration on the tolerance side of the balance (Fig. 4, *D*). A child's tolerance may be increased, for example, by immunizing injections with house dust or pollen extracts, provided they are among the specific causes of his asthma. The safest situation for a patient is that in which tolerance has been increased and the allergic load reduced to a minimum by elimination procedures. This gives him the greatest margin of safety.

Often it is not possible to get rid of *all* of *every* antigen to which a child is sensitive. Fortunately, removal of those sources which *can* be eliminated and reasonable avoidance of the rest will often suffice to bring exposure within the patient's tolerance. This concept applies particularly to house dust, about which a mother is likely to comment, "But you can't possibly get rid of *that*."

The diagrams also illustrate the aggregate effect of multiple allergens, which individually would not cause asthma. For example, asthma may occur during timothy season in a boy who explored a dusty basement after having ingested some chocolate candy. Assuming him to be sensitive to timothy pollen, house dust and chocolate, no one of these alone may have been able to precipitate asthma, whereas the combination of all three was able to do so (Fig. 4, *B*).

The balance diagram does not illustrate the usual essentiality of adequate *specific* causes for the precipitation of an attack of asthma; it does not emphasize the fact that precipitating factors *by themselves* usually do not cause asthma. This concept is better illustrated by the analogy of a loaded gun in which the bullets are allergens (house dust, dog or cat hair, feathers, and so forth) and the trigger-movers are precipitating factors (respiratory infection, odors, and climatic or emotional factors). Removal of the bullets will prevent an explosion (asthma) even though the trigger is pulled.

In applying both analogies to the patient—the balance and that of the loaded gun—it should be remembered that each may proceed in "slow motion" and that there may be, therefore, a lag period before symptoms become manifest.

CONTINUITY SYMPTOMS

A child who has attacks of asthma usually has allergic rhinitis as well. The allergens which irritate the mucous membrane of his lungs usually irritate his nasal mucosa and cause him to sneeze and to have an itchy nose. Such identity of etiology of the patient's asthma and his allergic rhinitis can be used in several ways:

1. It can aid in establishing the *diagnosis* of asthma, since other forms of noisy breathing and coughing are not apt to be associated with excessive sneezing and rubbing of the nose.

2. It can aid in establishing *etiology* for asthma, since whatever initiates sneezing or itching of the nose is very likely a factor in the patient's asthma.

3. Perhaps most important to the physician, these minor symptoms of allergic rhinitis can be used as a guide in *treating* the patient's asthma. Infrequent occurrence of asthma attacks need not force the physician to postpone his decision on the effectiveness of his program for the control of asthma. Improvement, or lack of it, in the nasal symptoms is likely to be a reliable guide; and since nasal itching and excessive sneezing are usually present day after day, rather than intermittently, they afford a continual guide to therapy. Their presence gives *continuity* to the patient's symptomatology which may otherwise be lacking, owing to the intermittent characteristics of the asthma.

Often other *continuity symptoms* are present in a case of asthma. These are the minor symptoms of asthma itself and include coughing at night, and coughing or wheezing on exertion. A child who is reported to have only occasional *attacks* of asthma may have these minor symptoms most of the time. If so, they too can serve as a therapeutic and diagnostic guide.

In many instances asthma is mistaken by the mother, and occasionally by the physician, for infection of the upper or lower respiratory tract. The history the mother gives is of "one cold after another," occasionally followed by bronchitis or even pneumonia (Fig. 5). This con-

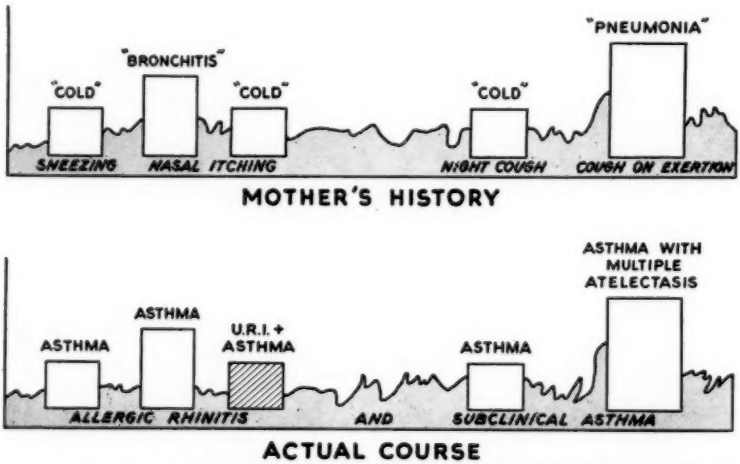

Fig. 5. The mother's interpretation of asthma may be that her child has repeated "colds," some of which are followed by bronchitis or pneumonia. When an upper respiratory tract infection *does* occur, it may be accompanied by asthma and thus resemble previous attacks. Linking episodes of asthma together are the "continuity" symptoms of allergic rhinitis and subclinical asthma.

fusion of allergy with respiratory infection is easy to understand, since their symptomatology is similar: cough, nasal congestion and, at times, fever. It is not generally appreciated that asthma itself may cause some elevation of temperature. When mucosal edema, bronchial muscle spasm and mucus plugs combine to cause multiple areas of atelectasis, the clinical picture may so simulate that of bronchopneumonia as to make differentiation between primary asthma and primary infection difficult even for the alert physician. In such instances temperature elevation may be considerable, and a low grade infection dependent upon the abnormal lung physiology actually may be present. When the mucus plugs are relieved and normal aeration re-established, such infection rapidly clears up, often without recourse to antibiotics.

The mother is further encouraged to think that "colds" and not allergy are the problem if her child, sharing an occasional upper respiratory tract infection with the rest of the family, has asthma as a result, and behaves exactly as he did when asthma alone was present.

ENVIRONMENTAL CONTROL

The Importance of Environmental Control

Most allergists in this country agree that house dust is the most frequent cause of asthma in children. Clinical sensitivity to house dust is not difficult to establish. It is usually associated with a clear-cut positive scratch test if a sufficiently concentrated extract is used.* A positive test usually signifies the presence of clinical symptomatology. As discussed under Continuity Symptoms, there usually will be a history of associated allergic rhinitis, sneezing, and itching of the nose. In the house dust-sensitive patient, for some poorly understood reason, these symptoms together with nasal congestion tend to be especially pronounced upon arising in the morning.

The exact nature of the house dust allergen has not been verified. One would expect a positive skin test to house dust to represent the sum of positive reactions to kapok, cotton linters, wool, cow hair in carpet pads and similar substances used in furnishing. Such is usually not the case; frequently all such tests are negative, while house dust is strongly positive. House dust in New York is similar to that in San Francisco and in all other cities in the United States. Because of this established similarity of the dust reaction throughout the country, most allergists feel that it is not necessary to obtain dust from the patient's home—so-called autogenous house dust—in order to study or treat their patients. House dust antigen is closely related to kapok and cotton linters—two botanically related vegetable fibers. Aging of these materials

* The 1:40 dilution of Endo House Dust extract may be used for scratch testing. Intradermal tests should never be done with this strength. (See also p. 693.)

in some way induces, and then increases, their antigenicity. One of the best sources for obtaining material for the preparation of commercial house dust extract is the kapok of old mattresses. The average American home probably contains more kapok and cotton linters than any other material except wood. It is easy to understand, therefore, the importance of controlling dust from these sources in the home of the house dust-sensitive patient.

To dispose of all sources of kapok and cotton linters in the home would be a large and frequently impossible order. Fortunately, this is rarely necessary. Strict attention to dust control in a child's bedroom will usually suffice to give a satisfactory result, especially if it is combined with injection treatment. Occasionally house dust control alone, with emphasis on the bedroom, will suffice to bring about adequate results without injection treatment. The reverse, however—immunization by means of house dust extract without elimination of dust sources, even in the bedroom—will lead to many failures. This is not surprising. It is apparent that a house dust-sensitive person who sleeps on two containers of the allergen to which he is sensitive—a mattress and a box spring—is a candidate for trouble. Yet this is what a great many known house dust-sensitive persons are doing.

Bedroom Dust Control

The bedroom is of paramount importance in dust control, and rendering it relatively dust-free produces rewarding results in the house dust-sensitive child. Roughly, half of his life is spent in this room. Out of 24 hours in each day, he sleeps 10 or 11 hours, and spends an additional hour or two dressing, playing or studying in it (Fig. 6). During the remaining 11 or 12 hours he is either at school or out of doors for a total of 8 or 9 hours. In these latter situations he does not encounter house dust. Dust from outside sources, roads and soil may be present in abundance, but the child is not allergic to this dust. The school contains little or no upholstery, draperies, carpets, pillows, sofas, stuffed chairs, mattresses or box springs—and these are the sources of house dust. Conversely, mud or soil in the child's bedroom does no harm at all. It is the contents of the vacuum cleaning bag of which he must beware.

Since the time spent at school and out of doors is a period of freedom from exposure to house dust, there are only about three hours of the day during which exposure to house dust can occur other than that in the bedroom. These are the few hours the child spends in the living room, watching television or eating meals. Some of this period, such as that spent in the kitchen, is in a dust-poor area.

It is seen that out of 15 or 16 hours spent in his home in each 24-hour period, a child will spend 75 or 80 per cent of this time in one

room—his bedroom. If this one room is properly dust-controlled, a great deal will have been done toward solving the house dust problem. An all-out effort toward this goal is fully justified. This will involve the removal of upholstered furniture from the bedroom, and encasing the mattresses or boxsprings which are allowed to remain—whether on the patient's bed or that of someone else. These encasings must be carefully made of durable dust-proof material. Plastic encasings are not satisfactory and not durable, and should not be used. Although rubber *mattresses* do not require encasings, rubber *box springs* do have some kapok or cotton linter upholstery—even though the upper portion may be sponge rubber—and they must be encased.

Feather pillows should not be used, but should be replaced by pillows of rubber, Dacron or similar material. Air heater inlets should be sealed closed, and, if necessary, an electric heater can be used to heat the bedroom. Wool carpets and hair or waffle pads should be removed; washable cotton throw rugs may be used in their place. Stuffed and fuzzy toys, unless made entirely of synthetic materials or rubber, are not permissible.

Finally, the bedroom closet should be cleaned out and not used as a storage area, and draperies and other dust catchers eliminated. Comforters or quilts, unless made entirely of synthetic materials, should not be used. Blankets made of cotton or synthetic fiber are best, but woolen blankets are often tolerated. They, like woolen clothing, are not continually pulverized into small dust particles by being walked on, as is the case with carpets.

Written directions for house dust control such as those which follow should be given to the parents of each house dust-sensitive patient, as well as an order blank* for the necessary encasings, which are made to measure and are not usually obtainable except from the manufacturer.

* Obtainable from Allergen Proof Encasings, Inc., 4046 Superior Avenue, Cleveland 3, Ohio, and Allergy-Free Products for the Home, 130 Livingston St., Brooklyn 1, N.Y.

Fig. 6. Twenty-four hours in the life of a child.

The parent should be instructed to give the child's bedroom an initial thorough washing down, and a weekly wiping down with an oiled or damp cloth.

HOW TO PREPARE A DUST-CONTROLLED BEDROOM

1. The room should contain only one bed of metal or wood. A couch or sofa with attached legs will not do. If a second bed is necessary, it too must be prepared as will be described, even though it is not occupied.

2. Remove all upholstered furniture, rugs, rug pads, pillows, stuffed toys, window drapes and dust-catching ornaments. Remove all stored clothing, toys, packages and other articles from the closet. The closet should contain only the patient's clothing in current use and should be as dust-free as the room.

3. Cover the mattress with a recommended encasing, *not* an ordinary plastic one. Ask for an order blank for the right type of encasing. If a box spring is used, although one is not necessary, it *must have a similar encasing.* A foam rubber mattress does not produce dust and so does not require encasing. Despite many salesmen's statements to the contrary, even foam rubber box springs contain upholstering material in part and must be encased. You may also be told that foam rubber mattresses are not available without box springs. This is not so.

4. Close and then permanently seal all furnace pipe outlets in the room. Otherwise the room will become filled with dust-laden air during the operation of the furnace. An electric heater may be used to heat the room.

5. Do not use comforters or quilts on the bed. Cotton, rayon or synthetic fiber blankets are best, but wool blankets are usually also tolerated. They may be used unless you are directed otherwise. Wool rugs, however, are not allowed, nor rug pads, except those made of rubber. Cotton washable rugs may be used if kept clean. A thin cotton mattress pad is permissible if washed frequently.

6. Pillows should be of foam rubber. Dacron or other synthetic fiber pillows may also be used. Do not use kapok, feather or down pillows.

7. Plain light curtains may be used at the window if kept dust-free. No drapes.

8. Move the bed and the remaining (*un*upholstered) furniture to the center, or out of the room, in order to scrub the room thoroughly. The entire room should have a thorough initial cleaning from top to bottom. Include the molding, lights, shelves, closets, walls, etc. Keep the room dust-free with frequent cleanings and a weekly wiping down with an oiled or damp cloth.

9. Do not allow the patient to nap or sleep elsewhere unless the bed has been prepared as above. A couch or sofa cannot be encased and, therefore, is not permissible. If the patient is confined to bed by illness, do not bring in extra kapok or feather pillows. When he visits or travels, he should take his rubber pillow with him.

10. If a child plays in a room other than his bedroom, it too must be dust-free.

11. Since dogs and cats are among the most notorious causes of allergic troubles, the patient should not live in a home where they are kept. If he is not already allergic to these animals, their presence invites the child to become sensitive to them.

The improvement which follows attention to house-dust in the bedroom can, if necessary, be increased by changes along similar lines in the living room and elsewhere. Feather or kapok pillows and old upholstered furniture are especially troublesome. The older they are, the more trouble they cause. Hair rug pads are also a source of trouble.

Shredded foam rubber, or Dacron or other synthetic fiber can be used to replace feathers or kapok pillows. Rug pads can be dispensed with or rubber ones used. Woolen rugs or rugs made from other types of hair can be replaced by cotton, flax, rayon or synthetic fiber rugs. Better yet, linoleum floor covering can be used.

These precautions should be continued for many years even though symptoms are absent.

Further Environmental Control

The program outlined for bedroom dust control may give fairly satisfactory control of a child's asthma. Further benefit can often result from an extension of the same principles of control to the sources of dust elsewhere in the house. However, it is often necessary and desirable to add the additional benefit of immunizing injections with house dust extract and pollen extracts if the patient is pollen-sensitive. Trouble may arise, however, if the household includes a cat or a dog. To neglect to remove these notorious causes of asthma can result in failure of an otherwise satisfactory prophylactic program. The physician is fortunate if his asthmatic patient does not already have a pet dog or cat; he can then warn the parents against obtaining either one. But if this is not the case, he has a difficult problem on his hands, and much may depend on how he handles it. If the patient is sensitive by scratch or intradermal test to dog or cat hair, there is no question about the need for disposing of the animal. If the patient lives in an urban community and the pet has had access to the house, it is unlikely that a plan to keep the pet "outside" or "in the basement" will ever succeed. To try to separate a child and the family pet in this manner is unrealistic.

Failure to dispose of the pet to which the child has a positive skin test is to ignore the purpose for which the test was done—to determine the causes of the child's asthma in order to control it. Positive tests in the house-inhalant and epidermal group are almost always associated with clinical symptoms. Immunizing injections to animal dander without elimination of the animal are no more successful or logical than treating a patient with house dust extract without taking steps to eliminate such dust.

It should be remembered that when the scratch test to dog or cat hair is negative, the intradermal test may be positive. Not all testing material is sufficiently potent to reveal clinical sensitivity by the scratch test. It is not so easy to make a potent extract to animal hairs and dander as it is to prepare satisfactory test material to pollens or house dust. But even when the intradermal test to dog or cat is negative, a serious problem still remains:

1. Clinical sensitivity may be present despite the negative test.
2. If sensitization has not been established already, it may occur at any time in the future. The child is never allergic to a dander on his *first* encounter with it; sensitization must first occur. It is only *after* sensitization has occurred that there is trouble.

Prophylaxis against such sensitization, by removal of the dog or cat, is certainly justified. Few of us would think it logical to have our house dust-sensitive patient sleep on a feather pillow—another notorious source of asthma—simply because the skin test was negative to feathers.

It is no more logical to permit a child to have daily indoor contact with a cat or dog if he has already demonstrated his capacity to become allergic to other types of household allergens.

On the wall of our Children's Allergy Clinic at the University of California School of Medicine we have a sign which reads, "Children with asthma are not allowed to have feather pillows, cats or dogs." It does *not* add, "if the skin test is positive." The problem of asthma in childhood is sufficiently serious to warrant this attitude. We are convinced many patients have been helped and few have been harmed by implementing this policy. Only in cases of purely seasonal pollen asthma, or pure food or bacterial allergy, have we relaxed our rules.

If a family lives in the country and owns dogs which never gain access to the house, the situation is different. Such animals are more nearly the equivalent of neighbors' pets, contact is much less intimate and prolonged, and sensitization is much less likely to occur. The dander and hair of outdoor animals do not accumulate as they do with indoor pets, and cause much less trouble.

Other Techniques for House Dust Control

There is no substitute for removal of the sources of house dust. Other measures are only adjuncts. Dust filters are of limited value; if they are used, they should not be substituted for any of the precautions already mentioned. Electrostatic dust filters are much the most efficient, but expensive. When the dust problem is a serious one, they may afford real assistance.

The use of liquid preparations* to retard the liberation of dust from rugs and upholstered furniture is also a poor substitute for the actual removal of sources of dust. The application of such liquids can be laborious and expensive and leave the question undecided as to how much has been actually accomplished. I do not recommend them.

On the other hand, it is often worth while to hire a commercial firm to clean out heating ducts which have accumulated a large amount of house dust and lint which cannot otherwise be removed.

At the University of California Children's Allergy Clinic, the staff makes a home visit to inspect the bedroom and home of each house dust-sensitive patient after a suitable opportunity has been given for carrying out the printed instructions each patient receives. Such a visit often reveals errors or omissions, the correction of which is of value to the patient, and the presence of which may help explain a poor result. The visit also has considerable psychological value, since it emphasizes to the parents the importance we attach to the entire program.

* Marketed under the trade names of Dust Seal and Allergex.

CONCLUDING COMMENTS

The emphasis given at our Children's Allergy Clinic to environmental control, as outlined in this article, is based on the results it has produced in our patients. We usually delay injection treatment until our directions have been carried out and an inspection visit to the home has been made.

In this way the benefit of the control program is more easily recognized and its importance more readily appreciated. We are not too academic in interpreting skin tests. If house dust alone gives a convincingly positive skin test which is supported by the clinical history, we believe that the entire program of environmental control is indicated, including avoidance of pets. If *one* epidermal substance, such as wool, feathers or rabbit hair, gives a positive reaction by skin test, we believe that other epidermal substances are likely to be, or to become, sources of trouble. Thus, if cat hair is positive, we are not persuaded that a dog is acceptable because the test to dog hair is negative.

One final word of caution: As in all treatment programs, results will depend upon recognizing to which patients the program applies. Environmental control is not likely to be of help in cases of pure food allergy, pollinosis, bacterial allergy or nonallergic conditions such as fibrocystic disease. However, about three out of four asthmatic children are allergic to house dust, and, in them, the program has given invaluable assistance.

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USE OF STEROIDS IN ALLERGIC RESPIRATORY DISEASES IN CHILDREN

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The usefulness of the steroid drugs and corticotropin in the treatment of children having allergic disease of the respiratory tract has been well established. Nevertheless, some physicians still are puzzled about how and when to use these agents. This is illustrated by the recent remark of a parent of one of my patients: "My home doctor gave Johnny a shot of one of the new miracle drugs, and when it didn't help, he said that there was nothing more that could be done."

If these drugs are used only when really necessary, in adequate doses and for a period no longer than essential, and if the child is carefully supervised during the period of administration, the results should be gratifying and the unpleasant reactions minimal.

MODE OF ACTION

It is perhaps trite but nonetheless wise to remind the reader that corticotropin (ACTH) is a pituitary hormone that stimulates the adrenal. Its clinical effect is the same as that of the steroids as long as the patient's adrenal glands can respond to this stimulus. The steroid drugs are the adrenal hormones or closely related chemical compounds that act because of their chemical configuration and are active whether or not the patient has normal adrenal function. Children with allergic disease apparently have no reason because of their allergies to have depressed adrenal function. However, severely ill children who have asthma may not respond at times in the expected fashion to the use of corticotropin.

Corticotropin and the steroid hormones have many physiologic and pharmacologic actions. This discussion will be limited to those related

to allergic phenomena. These hormones are thought in this regard to have three principal actions: namely, (1) interference with the formation of antibodies, (2) modification of histamine metabolism, and (3) an anti-inflammatory (antiphlogistic) effect. Other actions both presently known and unknown also may be important.

The effect on production of antibodies is poorly understood. Experimental work[4, 5, 9, 22] suggests that antibody production is suppressed while the animal is being treated with hormone and that the hormones must be given during the adaptation stage, not the production stage, of antibody synthesis. Furthermore, it is evident that the concentration of circulating antibody in the rabbit may be decreased by interference with the production of antibody, but not by its increased destruction. However, the doses required to suppress antibody formation in animals are large, and comparable doses in man would be far beyond those usually given in clinical medicine.[6]

Rat skin[14, 26] and perhaps human skin[18] depleted of histamine regain it very slowly while the subject is being given cortisone systemically. A patient suffering from severe allergic disease who receives a steroid drug excretes increased amounts of free histamine in the urine shortly after he has improved symptomatically.[23]

The anti-inflammatory effect is on the capillaries in the end-organs.[6] This action is a local one at the site of the inflammatory response and is not the result of systemic mechanisms. The greater the amount of inflammation, the larger is the dose of steroid necessary to combat it. However, evidence is against the immediate parallelism between a high concentration of steroid hormones in the blood and clinical improvement.[3, 7, 13, 25]

I strongly suspect that the anti-inflammatory action is the most important one, but there is no universal agreement about this.

UNTOWARD REACTIONS

The untoward actions, which perhaps are better called the "physiologic actions of the steroids that we do not desire," should be constantly borne in mind by the physician prescribing these drugs. Although the incidence of these undesired reactions has decreased with the synthesis and marketing of new compounds, every steroid preparation now commercially available has produced undesired effects. As the potency of the effects against acute inflammatory changes of some of the synthetic steroids has been increased, as in prednisone, prednisolone, methyl prednisolone, triamcinolone and dexamethasone, it is true that the objectionable effects of sodium retention and potassium loss have been decreased.

When cortisone or hydrocortisone is used for more than a week, a low-salt diet should be given, and 1 gm. of potassium chloride should

be given daily, although such regulation is usually not necessary with the other steroids now in current use. Likewise, the effects of these agents on the gastrointestinal tract and on the psyche and the production of obesity have been decreased, but not completely eliminated. Anyone who contemplates using a steroid drug for a prolonged period should read the special article by Good and associates,[12] which deals with the use of cortisone and corticotropin.

When a steroid drug is to be administered to children for a prolonged period, the effect on growth must be considered. Hill,[17] in 1955, reported that 24 of a group of 43 allergic children ranging in age from 6 months to 12 years showed some retardation of growth, but that this effect was not great when the dose was 25 to 75 mg. per day. Blodgett and co-workers,[1] in 1956, studied 36 children undergoing prolonged treatment with cortisone; 20 of these children had allergic disease. They related the dose of cortisone to the surface area of the body and found that a dose of 45 mg. per square meter per day or more given over a period of a few weeks would slow the rate of skeletal growth in these allergic children; subsequently, however, there appeared to be a compensatory spurt of growth when the dose was reduced below the suppressive level or when use of the steroid was stopped. They tentatively concluded that treatment with cortisone may not alter the child's potential ultimate stature. Niermann and Van Metre[24] recently reported that asthmatic children who received 7.1 mg. or more of methyl prednisolone per square meter per day for 6 months or more had an increase in height of only 17 to 60 per cent of the expected normal rate; children receiving 5 mg. or more of prednisone per square meter per day attained from 0 to 80 per cent of the expected gain in height.

The synthetic steroid introduced most recently, namely dexamethasone,[2] has by far the most potent anti-inflammatory action of any of the presently available drugs, but it does produce a significant and sustained negative calcium balance. Such an effect was reported earlier in adult asthmatic patients treated with cortisone.[19] In this latter study on cortisone increased excretion of calcium was noted in the urine, whereas the negative balance in patients treated with dexamethasone apparently was due to increased fecal excretion of calcium. This information was obtained from study of adults who had arthritis. Patients with Cushing's disease do not have an unusually high fecal excretion of calcium.[15] Administration of cortisone has produced an increased fecal excretion of calcium only in adult patients with sarcoidosis[15] and in infants having idiopathic hypercalcemia.[21] The use of dexamethasone in children must be carefully studied before its long-term use may be considered safe. It appears entirely probable that dexamethasone in doses large enough to cause a suppressive effect on asthma will have a limiting effect on growth as well.

The intermittent oral use of prednisolone (3 successive days of treat-

ment followed by a 4-day rest period) in 37 severely allergic children over a 2-year period produced evidence of decreasing adrenal function in these children as measured by the impaired ability of each patient to respond in a normal manner to administration of exogenous corticotropin.[27] The greatest decrease was noted in children receiving the largest doses. No serious clinical complication of the steroid therapy was noted.

When chickenpox develops in children who have been receiving steroid drugs, the disease is unusually severe, and some of these patients have died.[13] It is best to discontinue use of these drugs as promptly as possible if patients have been exposed to varicella. Children having arrested tuberculosis should be given steroids only when concomitant antituberculotic chemotherapy is given. Children who have duodenal ulcers or diabetes should receive steroids only under careful supervision.

Finally, attention should be called to a state of adrenal suppression that occurs in patients whose adrenal status was normal before treatment with the steroid drugs. In our institution my colleagues and I assume that significant suppression has occurred when the following doses have been given to adults or older children for 5 or 6 days or more: cortisone, 25 mg. or more per day; hydrocortisone, 20 mg. or more per day; prednisone, 5 mg. or more per day. In smaller children, smaller doses likely will produce suppression. Some suppressive effect will last for three to four weeks after administration of the drug has been stopped; in some patients this effect persists for several months. We do not believe that corticotropin is of value in reactivating this depressed function.

This decreased adrenal function must be considered if the patient is to be subjected to a surgical procedure. It is our practice to give 200 mg. of cortisone intramuscularly on each of 2 days before operation and 100 mg. on the morning of operation. The need for steroids in the postoperative period depends on the patient's course. During an uneventful convalescence none will be needed, and it is not necessary to "taper off" the dose of steroid unless the child is receiving steroid treatment for allergic disease at the time of operation. If emergency surgical treatment is necessary or if the afore-mentioned dosage does not prove adequate, hydrocortisone sodium succinate or prednisolone sodium hemisuccinate may be given intravenously. Similar treatment should be considered when a child receiving steroids is severely injured or has a serious illness.

AVAILABLE STEROID DRUGS

It should be stated at the beginning of this section that this material may be out of date by the time the article goes to press because of the continuing introduction of new compounds for clinical use. Table 5

TABLE 5. *Some Presently Available Steroid Drugs*

U.S.P. NAME	PROPRIETARY NAME	EQUIVALENT ORAL DOSE
Corticotropin	Acthar	For intramuscular use;
	Actrope	no equivalent oral
	Cortrophin	dose
	Depo-ACTH	
	Solacthyl	
Cortisone acetate	Cortivite	25 mg.
	Cortogen acetate	
	Cortone acetate	
	Isopto cortisone	
Hydrocortisone	Cort-Dome	15–20 mg.
	Cortef	
	Cortril	
	Hydrocortone	
	Otosone-F	
Prednisone	Deltasone	5 mg.
	Deltra	
	Meticorten	
	Paracort	
Prednisolone	Delta-Cortef	5 mg.
	Hydeltra	
	Meticortelone	
	Paracortol	
	Prednis	
	Sterane	
	Sterolone	
Methyl prednisolone	Medrol	4–5 mg
Triamcinolone	Aristocort	4 mg.
	Kenacort	
Dexamethasone	Decadron	0.75 mg.
	Deronil	

lists many of the drugs presently available, together with their chemical names and their relationships to dosage.

Most of the preparations of these drugs are available only for oral use. Hydrocortisone and prednisolone are available for intravenous administration. Cortisone, hydrocortisone and prednisolone are available for intramuscular injection. Corticotropin is also available for either intravenous or intramuscular use.

USE OF STEROIDS IN ALLERGIC DISEASE

Nearly all children who have allergic disease may be benefited symptomatically by the use of steroids. The task of the physician is to decide in which child their use is necessary and to give them in such a way that the patient will be benefited and not harmed.

Hay Fever

A few children with hay fever apparently cannot have their disease sufficiently ameliorated by the usual means of environmental control, hypo-

sensitization and the use of antihistaminic and sympathomimetic drugs.

Experimental trial has suggested the therapeutic value of hydrocortisone or prednisolone used as snuff.[11, 16, 20] Administration of these drugs in this fashion apparently avoids any systemic side reactions. To the best of my knowledge, however, none of this material is commercially available as yet for use as snuff. A liquid preparation of prednisolone for use as a nasal spray is available.

In an occasional child who is having great difficulty with hay fever systemic administration of steroids is justifiable. Once instituted, such therapy should be continued throughout the pollen season. The dose will vary with the size of the patient and the severity of the disease. I have not yet had to use steroid drugs for this purpose.

Children with nonseasonal hay fever (vasomotor rhinitis, perennial allergic rhinitis) only rarely should be given steroids. The use of steroids causes complete involution of nasal polyps, which are a complication of vasomotor rhinitis. However, the polyps usually recur on cessation of treatment unless the causative factors have been determined, environmental control instituted and, often, hyposensitization treatment started.

Asthma

Among children who have allergic disease of the respiratory tract, it is those suffering from severe or prolonged asthma for whom treatment with the steroids is usually considered. Relief is obtained in 6 to 72 hours, depending on the severity of the disease and the dose of steroid given.

Some patients who have asthma caused by sensitivity to pollens may require use of steroids also. If such treatment is instituted, the administration should be continued throughout the rest of the pollen season, which is seldom more than a few weeks, thus limiting the duration of treatment.

Children suffering from perennial asthma, however, present a year-long problem of treatment. In a few instances maintenance doses of steroids are necessary to keep the child comfortable and relatively free of dyspnea. In most instances, however, use of these agents is best restricted to "bailing out" treatment. Simply because a steroid has been necessary once does not mean that its emergency use inevitably will be required for every acute attack. One should make every effort to avoid the regular long-term use of steroids.

Finally, *steroids do not produce the prompt relief that nearly always follows use of epinephrine.* One should first give epinephrine in two or three small doses to institute the treatment of severe asthma unless the child is "epinephrine-fast" or has adverse effects from its use. Oral medi-

cation with steroids then can be started concomitantly, and, during the first 24 hours, further doses of epinephrine or other drugs can be given until the beneficial effects from the steroid drugs appear.

Dosage

Perhaps the best rule is that the dose be enough: namely, enough to produce a beneficial effect on the patient. Both the size of the patient and the severity of the disease help determine the dose. It is better to give a larger dose than might be considered necessary than to give too small a dose.

A number of dosage schedules have been proposed. I agree with Glaser[10] that prednisone should be given in an oral dose of 10 to 15 mg. every 6 to 8 hours for the first 24 hours and that the dosage should be reduced by 2.5 to 5 mg. per dose every day thereafter until its use may be discontinued or a maintenance dose is reached. We also have given 4 to 6 mg. of triamcinolone every 6 to 8 hours.

The intravenous use of hydrocortisone sodium succinate or prednisolone sodium hemisuccinate may be necessary. One should give 100 mg. of hydrocortisone or 30 to 50 mg. of prednisolone in 1 minute. Subsequent doses may be indicated. Since the intravenously administered drugs apparently do not produce a favorable effect any more quickly than those given orally,[25] use of the intravenous route should be restricted to those children who are vomiting or who refuse oral medication. Steroids given orally or intravenously act more quickly than those given intramuscularly.

For the occasional child with asthma who requires steroid therapy on a long-term basis the dose must be strictly individualized. Oral doses usually are better given about every eight hours. As the patient improves and often requires less of the steroid, a daily dose or one every two or three days may suffice. Intermittent treatment may be used in some children. Every effort should be made to stop use of the drug as soon as possible.

A recent report[8] suggested that prednisolone and hydrocortisone suspended in a freon propellant had a beneficial effect on adult patients having asthma. The most noticeable subjective effect noted was relief of cough and irritation. These favorable results apparently were caused by the local treatment and not by absorption of steroid and a subsequent systemic effect. A trial of this form of treatment in children who can be taught the use of a nebulizer appears worth while. One such trial in which a solution of hydrocortisone hemisuccinate was used failed to help more than 21 per cent of the 29 children treated.[28] The status of such treatment at this time should still be considered experimental.

SUMMARY

The steroid drugs have been an excellent addition to those agents available to the physician for the symptomatic treatment of allergic disease of the respiratory tract in children. Before prescribing these agents, the physician should familiarize himself with their mode of action and the possible undesirable physiologic effects. He should make sure that their use is really necessary by asking himself these questions: (1) Does the seriousness of the child's condition justify the use of steroids? (2) Have all other drugs for symptomatic use been properly given without benefit? He then should make sure that the dose is adequate, that the use of the drugs is stopped as soon as possible, and that the child is carefully supervised during the period of administration.

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INSTITUTIONAL TREATMENT OF ASTHMATIC CHILDREN

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The institutional management of asthma is almost entirely confined to a portion of those children who continue to have severely chronic asthma despite the best forms of treatment. The incidence of such chronic intractable bronchial asthma must vary rather widely, and there are some eminently fortunate physicians who have never encountered it, while others have recognized a fairly large percentage within their practices. Undoubtedly, the skills and experiences of the physician managing a case of bronchial asthma will do much towards averting the occurrence of the chronic and intractable pattern. Even the most eminently qualified and skillful physicians, however, will eventually encounter cases of bronchial asthma in childhood which are fated to be intractable despite all the best efforts at total management. It is with this population that we are concerned, and for whom the plea was made for a "home" as a restorative measure.[11]

In that first study on this subject, which pioneered an ever-increasing interest in the establishment of institutions for management of the disease, there were 41 cases of chronic asthma, approximately 10 per cent of a series of 425 children, all of whom had been subjected to accepted standards of modern investigation and treatment. These were patients at the Children's Allergy Clinic of the Mt. Sinai Hospital in New York City; and, of course, the incidence may vary in other clinic or private practice settings. In that study Peshkin reported the now familiar observation that removal of a child in a condition of "status asthmaticus" to a hospital ward frequently resulted in complete relief of all symptoms of asthma within the first three days of admission. Such improvement was thereafter maintained for the duration of stay,

only to be followed by recurrence within a few days of return to the home environment. This observation has been frequently recorded and has been variously explained as resulting from (1) removal from a continued exposure to an environmental allergen, or (2) elimination of an excessive interpersonal tension within a home, or (3) simultaneous improvement of the impact of environmental, emotional and allergic factors.[10]

HISTORICAL BACKGROUND

The Jewish National Home for Asthmatic Children had its origin in 1907 as a home for the care of well children of the tubercular poor. In 1940, ten years after the publication of Peshkin's first communication, the Board of Directors of the National Home for Jewish Children invited Dr. M. Murray Peshkin to design a program for rehabilitation of the child with intractable asthma, based upon separation of the child from the parents' environment and the home environment, and his removal to the institutional program at the Denver Home. A number of changes in the development of the program thereafter were implemented with what appeared to be increasing measures of success in the control of the condition. The facilities at the Home in Denver were expanded to permit the care of 150 children, and, to emphasize a nonsectarian policy, the name was changed in 1953 to The Jewish National Home for Asthmatic Children. After trial periods of direction by group workers and social workers a medical director on a full-time basis was appointed in 1954; and the medical, psychiatric and sociological programs were integrated, improved and expanded since that time. During 1957 the Board, under the guidance of its Chief National Medical Consultant, Dr. Peshkin, and its Chief National Research Consultant, Dr. Harold A. Abramson, expanded interest in the field of research and, with the aid of a grant from the United States Public Health Service, proceeded with the construction of an Institute devoted to research, primarily in asthma, but also in other related allergic diseases, this to be known as the Children's Asthma Research Institute and Hospital. The present Medical and Research Director was appointed in July, 1958, and was charged with the responsibility of developing an increased medical and research program for detailed analysis of the problems of intractable bronchial asthma of children.

The succeeding portion of this presentation will endeavor to describe the present organization of the Jewish National Home for Asthmatic Children. There is no intent to imply that this is the best organizational structure to develop for such a purpose, but only to indicate its present direction with full anticipation that there will be many revisions of structure and administration as experience determines.

The executive and consulting staff is deeply interested in the institutional management of this disease and is now engaged in an effort to assemble information about the existence of, facilities for, and program of institutions interested in the care of the asthmatic child in other parts of the world.

At least four institutions have been established in The Netherlands. One of these is a cheerful, one-story building with a wing containing adequate laboratory facilities, staffed by a psychiatrist, several young teacher-aides and a trained and experienced technician. Some 30 children are housed in the institution, and some studies are in progress, both from the point of view of allergic investigation and the psychologic problems presented by the children. There are at least two institutions under the direction of a pediatric clinic for allergic diseases in Copenhagen, one of these in Denmark itself and the other in Norway.[16] Another institution, located in Davos, Switzerland,[6] is supervised and occasionally visited by a pediatrician from London. Recently we received a communication from a physician charged with the responsibility of supervising such institutional care in Czechoslovakia, where there are at least four institutions serving varying needs of children in that country.[7] Correspondence contacts have been established with all these institutions.

In the United States a number of institutions, usually concerned with other institutional medical problems, have manifested interest in developing a program for the institutional care of asthmatic children and are presently in various stages of organizing that program and acquiring the staff to implement it. Such institutions, for example, are present in Denver (in addition to the Jewish National Home for Asthmatic Children), in Tujunga, California, in Tucson, Arizona, in the Atlantic City, New Jersey area, in Palo Alto, California, and also in Cincinnati, Ohio. These institutions accommodate from 15 to 65 children, usually in the 6- to 15- or 16-year age group; and one of them, at least, admits children in the infant group. They offer variable degrees of local educational opportunities, rehabilitation procedures of various types, and usually extensive facilities for psychologic study and care, in some cases of both parent groups and children; and some research is also in progress at some of the institutions. Most of the institutions are in their infant stages, and with increasing financial support, professional interest and expansion of facilities, there seems little doubt that activities will grow.

PHYSICAL FACILITIES AT THE JEWISH NATIONAL HOME FOR ASTHMATIC CHILDREN

The Jewish National Home for Asthmatic Children presently consists of 13 brick structures, situated on a 17½-acre tract of ground in a residential community within view of the foothills of the Rocky Mountains. Seven of these structures provide cottage dormitory facilities for the resident patients, and the remainder are administrative buildings, dining room, power plant, residence for attending physician or resident physicians, temporary hospital and research areas, and a building for the dental services, rehabilitation services, and group services, including therapy.

There are 150 children in residence at all times except for brief periods when there are discharges and admissions of new patients, usu-

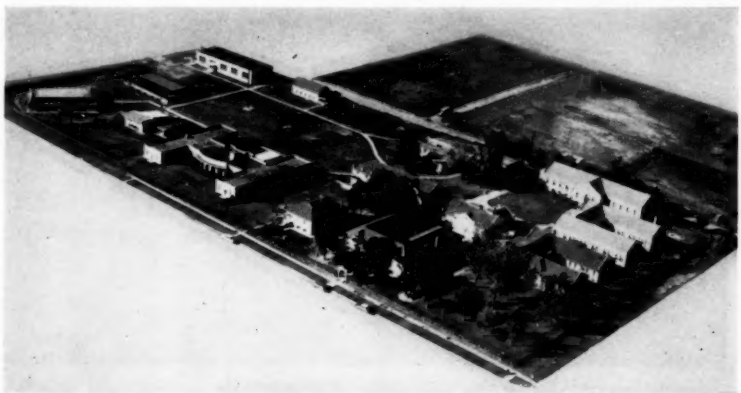

Fig. 7. Aerial view of Jewish National Home for Asthmatic Children. The first building of the Children's Asthma Research Institute and Hospital is under construction on the right upper third of the unoccupied ground area.

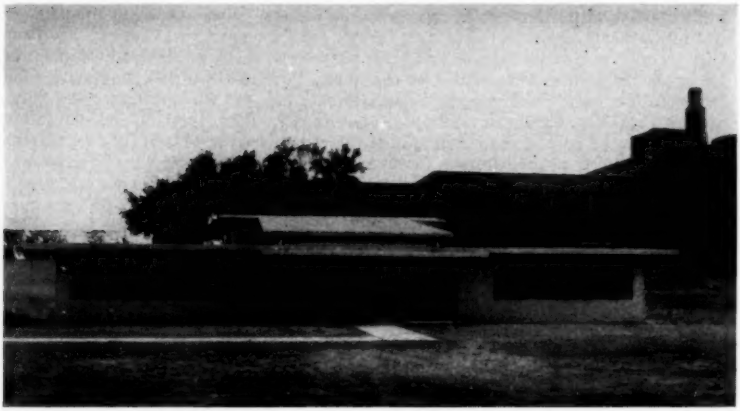

Fig. 8. A modern dormitory (foreground) for 16 children and 2 houseparents. In the background is the Lake Junior High School of the Denver Public School system, which is attended by seventh and eighth and ninth grade patients of the Jewish National Home for Asthmatic Children.

Fig. 9. View of the sleeping work space for a patient. In this particular dormitory there are 4 such spaces in each room, while in others there are accommodations for only 2 children in each room.

ally in relation to the school year and holiday periods. The children reside with houseparents who are carefully screened before selection and whose function is, as nearly as it is possible to do so, to create a warm, parental environment and supervision for the children during their residence. One of the newest of the dormitories houses 16 children in double bunks, two to a room, with a connecting double bathroom facility for each two rooms. There is a large, central, clear living area which occupies the main portion of the building, and the sleeping quarters open from the periphery, with a snack bar and full kitchen facilities towards the rear of the sitting room area.

STAFF STRUCTURE

An able and experienced administrative staff assists the Medical Director, headed by the Administrator, who assumes responsibility for maintenance of the physical properties and plant of the Home and for seeing that efficient physical arrangements are provided in all areas occupied by the children. He also represents the Home in contacts with the children's parents, pertaining to the child's custodial needs, such as allowance, clothing, various transportation requirements, and the like; and he makes all arrangements for receiving the child and returning him to his home area when maximum benefit has been achieved at the Home.

The Medical and Research Director assumes all responsibilities for functions relating to the medical care and rehabilitation of the child. This includes, in addition to the basic medical needs and the special allergic management, psychodiagnostic and psychotherapeutic services, which are an important part of the medical program. There is a special interest in the emotional problems of the patients and their families because the intractable asthmatic child referred to the Jewish National Home for Asthmatic Children from all parts of the country by competent physicians has already received all forms of allergic and other medical management with no significant benefit.

EDUCATIONAL AND RELIGIOUS GUIDANCE

The children admitted to the Jewish National Home for Asthmatic Children obtain their education at the Denver public schools, and the closest possible contact is maintained among the staff personnel of the Home and the educational administrative authorities in the respective schools. Many of the children admitted to the Home have had various kinds of difficulty at schools attended in their home communities, frequently because of extended absence occasioned by recurring or continuing episodes of asthma. In some there are additional emotional

blocks with respect to attendance at school, and in a smaller number actual functional mental handicaps, short of mental retardation, contribute significantly to a failure of normal or average adjustment. Whenever necessary, the houseparent gives special tutorial assistance to the child; and there are frequent conferences between the houseparent, the psychologist, and the school authorities or teacher, concerning the specific problems of an individual child, during the course of which the psychologist and houseparent, together with the physician in charge of the case, bring forth information that may assist the teacher in integrating the child to the group in school. In return, information of great value is given by the teacher as to the areas of education which need strengthening in a given child. These are, of course, one of the most important adaptive functions of the child, and a great deal of attention and effort is put into this area.

A number of children admitted to the Home have significant speech problems which vary from the mild to severe. Every effort is made to evaluate the speech defect and classify it, and for this purpose a speech therapist is employed by the Home who regularly sees all the children with these defects. There is especially close cooperation between the speech therapist and the psychologist in this regard, since many of the speech difficulties have an emotional or psychologic basis.

A fully equipped occupational therapy setup is also utilized for the correction of postural defects and for the strengthening of those areas of skeletal structure which are defective, using the best methods available for this purpose. These include not only breathing exercises, which are frequently utilized by groups interested in rehabilitation of the asthmatic child, but also other physical activities individually adapted for the child's needs.

The religious and spiritual guidance of the children is not neglected; in fact, it forms an important part of the over-all management of the child. Somewhat more than 50 per cent of our children are of non-Jewish faith, and one of the houseparents acts as co-ordinator of non-Jewish religious activities and sees to it that appropriate measures are taken to bring the child to Sunday School classes and to religious services as required by his particular denomination. The children who are Jewish are offered special opportunities for pursuing Hebrew education and for attending seminar classes in the Hebrew religion on the premises and are also taken to neighboring synagogues for the Sabbath services and for the various holiday worships.

At all times an effort is made to strengthen the role of the houseparent in a manner best designed to recreate for the child during his residence the feeling that there is indeed a parent surrogate who functions in all respects as does the true parent. This is a matter for continuing re-examination and research, since it is obvious that the estab-

lishment of such a psychologic and emotional relationship with the child can only be an approximation. Every effort is made, however, to make that approximation as nearly perfect as possible.

ORGANIZATION OF THE PROFESSIONAL STAFFS CONCERNED WITH THE CLINICAL SERVICES

Medical Service

The medical services are directed by the Medical Director, who presently has on his staff two senior staff pediatricians who have had a number of years of pediatric training. These senior staff pediatricians assume complete responsibility for the medical care of a designated population of patients and are assisted in the multitudinous functions involved therein by Fellows in Pediatric Allergy. There is a rotation of night time resident service among the junior and senior staffs, so that there is always 24-hour medical staff coverage at the Home to deal with any emergency as quickly as it may arise. This is considered a matter of the utmost importance, since the intractable asthmatic child may at any time have an alarming degree of severity in his symptoms, and it requires the prompt attention of skilled personnel to accomplish proper control. In addition to these full-time personnel, there is an attending pediatrician who specializes in pediatric pulmonary diseases. This physician makes regular rounds with the entire pediatric staff and with the Medical Director, and the problems of in-patients and of out-patients are discussed thoroughly, and a course of therapy outlined.

As indicated in Table 6, a large percentage of the patients arrive while still on maintenace dosage of the anti-inflammatory steroid drugs, and virtually 100 per cent of them have had the drugs at some time or another before admission to the Home. Table 7 reveals that some 50 per cent of these patients may have the steroid drugs withdrawn within the first 2 months of admission, and a small additional percentage in the 4 months thereafter. This leaves, however, what seems to be an irreducible minimum of children who continue to require steroids for a long time, many in former years for the duration of their stay. This is so despite the fact that frequent efforts are made to reduce and eliminate the steroids from the therapeutic armamentarium as soon as other therapeutic measures have been in use long enough to have become effective.

During the phase immediately following the withdrawal of anti-inflammatory steroid drugs, no matter how long the duration of previous therapy with these agents, it is considered essential to maintain close surveillance constantly. Children who are being started on steroid drugs or who require maintenance doses for long periods of time are also considered proper subjects for frequent clinical observation. These patients, therefore, are seen regularly by their senior physician at clinic

TABLE 6. *Incidence of Anti-inflammatory Steroid Therapy among New Patients Admitted to the Jewish National Home for Asthmatic Children*

	NUMBER	PER CENT	NUMBER	PER CENT
	7/1/57 to 6/30/58		7/1/58 to 3/31/59	
Total admissions	88	—	51	—
Previous therapy	65	75	49	98
Maintenance therapy on admission	44	50	26*	51
No previous therapy	23	25	1	2

* Three additional patients were on steroid therapy until 5 to 21 days preceding admission.

TABLE 7. *Rate of Discontinuance of Anti-inflammatory Steroid Therapy Following Admission to the Jewish National Home for Asthmatic Children (July 1, 1958, to March 31, 1959)*

Length of residence (months)	9	8	7	6	5	4	3	2	1 (or less)	TOTALS
Number of children admitted	6	3	2	3	5	1	5	—	1	26
Steroid therapy discontinued:										
1 month	—	—	—	2	2	1	1	—	1	7
2 months	3	1	—	1	2	—	2	—	—	9
3 months	1	—	—	—	—	—	—	—	—	1
4 months	—	—	—	—	—	—	—	—	—	
5 months	—	—	—	—	—	—	—	—	—	
6 months	1	—	—	—	—	—	—	—	—	1
7 months	—	—	—	—	—	—	—	—	—	
8 months	—	—	—	—	—	—	—	—	—	
9 months	—	—	—	—	—	—	—	—	—	
Still on steroid therapy	1	2	2	—	1	—	2	—	—	8

sessions on one of three days during the week, and every clinical and laboratory measure needed is used in order to maintain the most effective control with the minimum of side reactions and complications. In addition to these children on the steroid drugs, or who have had them recently discontinued, any child who has some special problem which has arisen and requires frequent surveillance is seen during these clinic visits.

From time to time the medical staff reviews and tabulates medical experiences and presents some phase of the general problem before an all-staff conference, preparatory to either designing a new line of approach in the management of the child or the creation of some set of clinical observations which may culminate in a better comprehension of one phase of the disease.

Psychiatric and Psychological Services

The psychiatric service presently consists of a staff psychiatrist and a consulting psychiatrist, the latter available to us for policy making and

special consultation functions. This service will shortly be increased in order to furnish adequate supervision to the psychological services, which presently are carrying the major case load for both diagnosis and therapy. The latter service is administered by a Director of Psychological Services, assisted by two senior psychologsts, respectively charged primarily with responsibility for (1) the organization of psychodiagnostic and psychotherapeutic services and (2) the development of research activities in this field, although each senior psychologist has both clinical and research responsibilities. Under these senior clinical psychologists there are several junior clinical psychologists. A training program for clinical psychologists has been approved for the Jewish National Home for Asthmatic Children and is operated under the Graduate School of the University of Colorado. The Psychological Services assume responsibility for training graduate students in diagnostic and therapeutic problems of the asthmatic child. Although this may seem like a somewhat elaborate psychological staff structure, it is, in fact, already inadequate to handle the varying straightforward clinical and especially the research needs of the program.

Every child admitted to the Home is seen shortly after admission by a senior clinical psychologist, together with the Medical Director and the assigned pediatrician, and the child's notions and attitudes explored in a general fashion. Misconceptions. misgivings and immediate moments of homesickness are dealt with at these levels initially, and in this regard the houseparent and the children with whom the new patient will take residence are also involved in the group adaptation function. The child is then referred for a complete psychodiagnostic survey, which may be performed in one to three sessions and includes an interview and the application of a battery of intelligence and projective tests. These are then evaluated by the junior psychologists and presented in conference with the senior psychologist, and a report describing the observations is drafted for the Medical Director's office for transmittal to the referring physician and agencies involved in the referral.

During this same period the senior pediatrician who had seen the child immediately upon admission makes a complete examination, and reviews all the findings on the referring physician's report. These are then assembled in a report to which are added observations during the course of residence within the first several weeks, response to group living, and the results of a complete re-evaluation of skin testing with inhalants and ingestants. A conference is then held by the medical staff, all the data are reviewed, and a tentative outline of therapy and program for the child is outlined. The Medical Director assembles all the data and sends them with his recommendations to the professional persons who referred the child to the Home. At the same time a letter

is written to the parents advising them that a report has been sent to their referring physician and suggesting that they contact him for an interpretation of findings to date. Thereafter the medical staff is responsible for providing bi-monthly reports on growth and nutritional development and the general health of the patient during his residence in the institution. There are, of course, frequent conferences with the psychological services as special events arise which are brought to the attention of the Medical Director, evaluated by the medical staff first, and then referred to the psychologist.

A great deal has been written about the psychological implications of asthma since the fine monograph published by French and Alexander[4] in 1941, and such articles as those by Rogerson, Hardcastle and Duguid,[14] Abramson,[1] Unger and Unger[15] and Hallowitz.[5] The general psychologic problems presented by the hospitalization of children with asthma and the psychosomatic study of allergic and emotional factors in children with asthma have already been referred to in the article by Long et al.[10] Blom[3] deals even more intensively with the problem of the reactions of hospitalized children to illness and refers to a study by Jessner et al.[8] which calls attention to the beneficial effects of hospitalization on the symptoms of asthma. All these communications refer to the intensely interesting and complex phenomena involved in the hospitalization of children for any chronic illness and the special characteristics of those hospitalized for asthma. The entire staff of the Jewish National Home for Asthmatic Children is completely conscious of and deeply concerned about these phenomena and cognizant of the beneficial effects alluded to (which indeed are borne out by long observations at the Jewish National Home for Asthmatic Children). The staff at the Jewish National Home for Asthmatic Children will continue its intensive study of all the psychologic aspects involved in adjustment of the child to separation from his family during residence in an institution geographically removed from the parental home.

A brief comment may be in order about the relative incidence of emotional phenomena or emotional disorder in children with asthma as compared with the incidence among children with nonasthmatic illness and among normal children. The difficulty in making such an assessment is emphasized in a communication by Lapouse and Monk[9] which was concerned with an epidemiologic study of behavior characteristics in normal children. This preliminary study evaluated the behavior characteristics of some 480 children as reported by mothers and was designed primarily as a testing device for an even larger project. Two rather significant findings emerged: first, mothers report, among their supposedly normal children, a high percentage of behavior commonly thought of as pathological; and, secondly, mothers' reports, in comparison with children's, tended to make errors in the direction of

under-enumeration, which suggested that the prevalence of the reported behaviors might even be higher than the data disclosed. The data revealed that 43 per cent of the interviewed children presented evidence of at least 7, and frequently more, fears and worries.

The purpose in calling attention to this article is to emphasize that much thoughtful planning and preparation is necessary to formulate proper kinds of objective test instruments. Only after applying these tests to normal and other control populations will it be possible to ascertain the incidence of emotional problems among hospitalized, chronically ill children. These tests, after the kind of critical formulation which Lapouse and Monk developed, might then be used for more sophisticated studies in an evaluation of the role of the methods of treatment themselves in an underlying disease and in the construction and development of the child's personality. Many of these developments may be independent of the disease itself, and careful study is required in order to separate that which is child per se and that which may be related to the illness or its treatment. At present the medical and psychological staffs of the Jewish National Home for Asthmatic Children, aided by the psychiatrists, are in the process of constructing just such test instruments for intensive future application.

Nursing Services

There is maintained on the premises a 19-bed, fully equipped hospital area, with individual rooms for the children who require hospitalization for acute illness; and with 2 rooms adjacent to the nurses' station, fully equipped for emergency medical care. The hospital area is staffed by a complete corps of nursing personnel who operate in the usual three shifts around the clock. The Director of Nursing, an experienced nurse in pediatric procedure and particularly experienced in the nursing care of the asthmatic child, sits in on many conferences which involve the over-all and general program of treatment outlined for the individual patient. She is assisted by additional registered nurses and licensed practical nurses as well as a corps of nursing aides and volunteer nurse assistants, who come from the Ladies' Auxiliary of the Denver area and from other volunteer sources supported and helped by the Denver Welfare Council.

Most of the children are hospitalized primarily for observation purposes and not generally because they are very sick. Frequently it is desirable to have a short isolation from the rest of the population for either a suspected or actual contagious disease. Facilities within the hospital area have been equipped for occupational therapy, play areas and other forms of entertainment to keep the children reasonably busy during their confinement period. The several pediatricians who are in

regular and constant attendance maintain their offices within the hospital area and are available at a moment's notice for any situation which may arise. The treatment room in the hospital area is fully equipped, and within it there are several compressed air outlets to which may be attached rubber tubings with valve arrangements and nebulizers of the most approved kind with which children may easily treat themselves during an asthmatic attack. The usual nebulized material consists of a mixture of Isuprel and Alevaire, but there are other combinations of inhaled bronchodilators which may be used at any time. The treatment room and the individual therapeutic procedure by any child are under the constant attention of a nurse supervisor.

A consultant in dermatology visits the institution at least once weekly, and he surveys all the patients presenting dermatologic problems. With the resident staff he prescribes treatment and may engage, as time goes on, in various kinds of investigative projects. Similarly, there is a fully equipped otorhinolaryngologic unit visited regularly by a consultant in otorhinolaryngology who follows up the many patients whose upper respiratory passages are infected and may be contributing to the perpetuation of the bronchial asthma.

LABORATORY FACILITIES

A fully equipped clinical laboratory is maintained in the hospital area and is staffed by two certified medical technicians. All procedures necessary to the proper diagnosis and evaluation of patients are carried out by these technicians. In addition, there is a qualified microbiologist, who presently is carrying out a careful evaluation of the bacterial infections. All probable pathogens are isolated and their antibiotic sensitivities studied. For epidemiologic purposes infecting agents are identified by immunologic or phage techniques. Ultimately, microbiologic methods using tissue culture and embryonated eggs and serodiagnostic methods will be used to help identify the viral infections occurring in this population of patients. It is considered that infection and its positive identification are among the most important factors which influence the intractable asthmatic child, and every useful method available will be applied to help understand the disease.

CLINICAL AND RESEARCH PROGRAM

The Jewish National Home for Asthmatic Children serves a number of objectives, and every specific function performed at the Home is considered to be simultaneously providing (1) a service to the patient, (2) a teaching facility for the entire staff of the institution, and (3) a research opportunity in the naturalistic sense that data must be carefully recorded and newer therapeutic methods so designed that later

careful analysis of the accumulated data will permit useful interpretation of the phenomena which affect the disease, asthma. Every member of the staff is constantly reminded of this and really operates on the premise that every function individually and collectively performed by the staff is a research activity. In this regard the many consultants who assist us with programming and with individual case analysis contribute thinking and direction to the various medical procedures.

For example, we consider that one of the most important functions we can perform is to establish the best possible objective criteria to permit evaluation of newer drugs and newer therapeutic procedures in the control of the asthmatic state. We are concerned not only with the relative effectiveness of one as compared with another bronchodilating agent, but also with the development of agents which may permit reduction of the dosage and indeed perhaps elimination of the use of the steroids, which, as indicated above, are frequently required in the management of the intractable asthmatic child.

Our laboratory facilities and our entire staff are constantly coming to grips with the critical appraisal of allergens, the methods of their preparation, the route of their administration for diagnostic and therapeutic purposes, and with the detection and quantitative enumeration of aeroallergens present in the environs of the Jewish National Home for Asthmatic Children. Attempts will be made to develop methods which may assist in the elaboration and fractionation of the most active and specific diagnostic and therapeutic allergen fractions which can be derived. Although we do not consider that immunologic approaches may solve all the practical and therapeutic diagnostic problems involved in the management of the intractable asthmatic child, or of other allergic manifestations, we believe that a large portion of the problems we face are indeed within this area and that they therefore merit the most serious consideration and careful, critical application.

It is also the desire of the executive staff of the Jewish National Home for Asthmatic Children that there be a close identification with the aims and objectives of the University environment, if the program is to achieve any kind of accomplishment. In this regard it is highly desirable that the program be approved by the sub-specialty board of the American Board of Pediatrics and the American Board of Internal Medicine. Every effort is being made to satisfy all the conditions essential to that accreditation. With respect to accreditation by the sub-specialty board in Pediatric Allergy, it is desirable and, in fact, necessary that an out-patient facility be created and that affiliate opportunities be presented for trainees for the care, evaluation and diagnosis of patients in the infant and younger age groups up to age six. Within the near future such facilities will be created at the institution, and, pending the actual creation of these facilities, an affiliated pro-

gram will be established either in Denver itself or in other areas of the country where accredited experiences of these kinds may be obtained by trainees. Possibly such measures will be in operation even by the time this publication appears.

ADMISSION POLICIES AND PROCEDURE IN THE MANAGEMENT OF THE CHILD AFTER ADMISSION TO THE INSTITUTION

All applications for admission to the institution are sent to the Medical Director. Applications are frequently initiated by a letter from the parents or relatives of a child detailing the harrowing experiences through which the family has passed. It is customary for the Medical Director to refer the parents immediately to their physician with the request that a short but incisive medical evaluation of the child be sent at once in order that a preliminary evaluation of the probable admissibility of the child may be made. Intractability of asthma, for example, may be defined in a number of ways, and since we are attempting to confine our admissions to the intractable asthmatic child, we have had to make some kind of simple working definition of this state. The definition includes resistant, persisting bronchial asthma with frequent loss of time from school, despite the application of competent, anti-allergic management, and good medical care for at least one year. Unfortunately, a number of persons who learn about the existence of the Jewish National Home for Asthmatic Children have the notion that the institution serves as a diagnostic and evaluative center; for the moment, at least, it does not. If the Medical Director feels that there is reasonable probability that the child satisfies the criteria of intractability, then he sends some rather detailed application forms to the physician and to the parents and a psychologic and social evaluation form usually to the referring physician with the suggestion that a local social agency be requested to assist the parents with completion of the form. In addition, forms are sent for completion by the principal of the school which the child has attended so that information can be obtained about the performance of the child in this most important area. In general, an effort is made to ascertain whether the child may be (1) psychotic, (2) mentally retarded or (3) delinquent. These are for the present the only three diagnostic situations considered inadmissible to the kind of group-living situation which has been created at the Jewish National Home for Asthmatic Children. It should be stated at once that the kinds of application questionnaire which can best serve the needs of an admissions committee are subjects for continuing investigation and indeed are the subject for constant review by our staff.

These completed forms are then assembled and carefully reviewed by the Medical Director. Frequently he will request that additional

psychologic and perhaps even psychiatric evaluations be obtained for the child before the application is considered sufficiently complete to present before the Admissions Committee. More frequently, because of a deficiency in the data describing the medical circumstances, the child will be referred for an evaluation by one of the 150 Regional Medical Consultants present in most populated regions of the country. Even more frequently he will request that the referring physician supplement his first report with more detailed medical data. After all these have been assembled and more specific information obtained, the entire application is presented to the Admissions Committee of the Board with the specific recommendation for either admission or rejection by the Medical Director. The applications are carefully weighed and reviewed from every possible angle before acceptance or rejection is voted.

The general attitude with respect to separation of the child from his parents is that we wish it were possible to have the parents available as well as the child. It is clear that in many instances the entire family situation must be dealt with rather than confining the medical care program to the child alone. The parents are often in considerable need of treatment by psychologists, social workers or psychiatrists, or all three. This does not necessarily imply, however, that the psychogenic problems of the parents are etiologic factors in the perpetuation of the asthma. It is probable, though, in any case, that alleviation of emotional disturbances will have a beneficial effect upon the control of asthma in the child, particularly after his return to the home situation. At every opportunity when parents come to visit the child an evaluation of their attitudes is made, and interviews are held with the Medical Director and the physician in charge as well as with the psychologist who may have been working with the child during his residence. However, it is certainly not practical to be resident in Denver at the same time the child is, and often removal of the child to the Denver area provides significant benefits to the parents in social, economic and medical ways. The opportunity to provide constant medical care without cost to parents whose resources have been severely depleted by their fruitless efforts at control is a very, very useful one indeed.

The therapeutic program which is prescribed is, as intimated above, directed by the Medical Director after a joint conference with his medical staff and with the Psychological Service. All medical, allergic, psychodiagnostic and therapeutic procedures possibly of benefit are utilized in the over-all attack on the control of asthma among this population of extremely resistant cases.

RESULTS

The best study of the results of therapy at the Jewish National Home for Asthmatic Children to date has been made by Peshkin.[12] He evalu-

ated differences among pollen-sensitive and nonpollen-sensitive asthmatics with respect to sex distribution, age at onset, and certain other vital statistics. His study of 150 intractable asthmatic children who had been sent from the New York area to the Home for periods ranging from 12 to 36 months, then returned to their parents, and thereafter studied for follow-up periods varying from one to 8 years was as follows:

The ratio of boys to girls was 2:1 for the entire series, and the peak age at onset of asthma was two to three years. Seventy-four per cent of the children of both sexes had onset of asthma before the age of six years. An analysis of the optimum duration of residence at the Home in order to obtain maximal continuing benefit after returning to their families revealed the following facts:

1. Seven and a half per cent of the children whose residence at the Home had been limited to 12 months failed to obtain relief from asthma (where failure was relief of less than 50 per cent);

2. One and a half per cent of the children who remained in residence at the Home for 18 to 24 months failed to obtain relief from asthma. All these children were returned to their families and showed a subsequent average incidence of recurrence of 3.5 per cent.

3. There were no failures among the children who had maintained residence at the Home for 30 to 36 months. After all the children had returned to their families the average incidence of recurrence rose to 9 per cent. Peshkin's conclusions were that "parentectomy" for 12 months for children with intractable asthma is inadequate for optimum rehabilitation after return to families and that the same procedure for 30 to 36 months for the more troublesome cases did not appear warranted because of the relatively high incidence of failure upon return home. "Parentectomy" for 18 to 24 months, however, appeared to be an optimum period for maximal rehabilitation after return home, and it was his recommendation that this be regarded as a practical period for "parentectomy." Incidentally, the average incidence of failure for the total series of 150 children was 1 per cent at Denver and 7 per cent after return to the families.[12]

These are the first published studies of their kind from the Jewish National Home, and any conclusions based upon these observations should be regarded as tentative but useful working guides to future study. In the future a concerted effort will be made to ascertain what factors are of primary importance in effecting persistent control of asthma after return of the children to their homes. The duration of stay may differ from one institution to another and may well change at this institution as our experiences with and analysis of the control measures increase.

The foregoing description of the organization and principles of management of the child with intractable asthma in an institutional setting

of the residential type should be considered only one example of the method of approach to this problem. There must be many other methods by which control measures are attempted, but, based upon an almost 20-year trial and error experimentation with several modifications of administrative control, these methods still seem to offer the most promise as a baseline upon which to develop the best program of institutional management of the intractable asthmatic child. Not enough emphasis can be placed upon the dominant concept of operation at the Jewish National Home for Asthmatic Children, i.e., that everything which has been done is as a learning procedure which will suggest future modifications of our administration.

Finally, no program can be considered adequate to the needs of so complex and so troublesome a disease as bronchial asthma if it is not scaled to an active and intensive research program. Therefore a word might be said about the scope of the research activities contemplated at the Jewish National Home for Asthmatic Children (I am certain that similar programs are in process or will, in the future, be initiated elsewhere as well). Asthma must be categorized and studied so carefully that in effect a life history of the disease under untreated circum-

Fig. 10. View of parts of two "asthmatic elevens." Scrimmages are arranged between better matched subjects than might appear from the picture. The expression on the opposition right end seems appropriate for the natural determination desired in rehabilitation procedure.

stances may be constructed. Every factor which may possibly contribute to the initiation and perpetuation of an attack must be chronicled, recorded, and ultimately correlated with all other vital data possibly concerned with the disease. At the Jewish National Home for Asthmatic Children methods are being developed by means of which we can codify all the significant biologic data of the asthmatic child which can then be assembled and placed upon cards with which a computer analysis may be made of probabilities of associations. A healthy, vigorous and critical program of clinical research by highly critical and well trained scientists, utilizing all the instruments which may be useful in control of the disease, will be in operation at all times. Much more important, however, is the construction of the facility (already described above) which will furnish opportunity to investigate the fundamentals of the allergic state and of the asthmatic reaction and its relation to the allergic state. This will surely involve many scientific disciplines, such as biophysics, biochemistry, immunology, microbiology, clinical medicine, psychiatry, psychology, statistics, mathematics, physiology, pathology, philosophy, and, if you please, every conceivable branch of reflective science and thought.

Dr. Frank Fremont-Smith aptly summed up the needs for a multidisciplinary approach to this problem in a diagram. Figure 11 is an adaptation of his diagram, but it clearly establishes that the relationship of man to nature is extraordinarily complex, and it makes no difference what specific area of that relationship is under investigation,

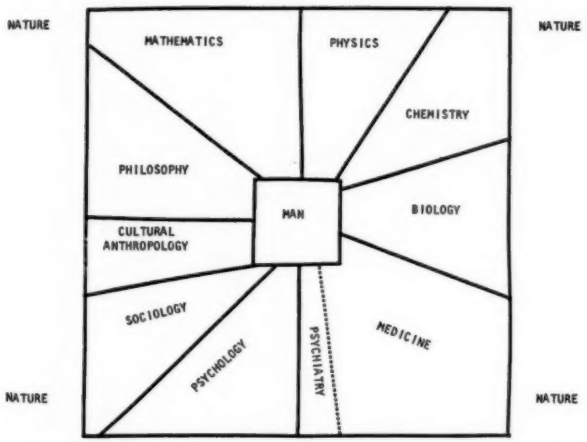

Fig. 11. The multidisciplinary approach to a study of man's relation to nature. (After F. Fremont-Smith: Address before the Second Seminar for Regional Medical Consultants, Jewish National Home for Asthmatic Children, Denver, Colorado, March 12, 1959.)

for a multidisciplinary approach to the solution of that relationship with free crossing of the artificial boundaries is absolutely essential if progress is to be made.

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CHILDREN WITH ECZEMA

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What does one do with an infant who is brought to him for "eczema"? He first tries to determine by the history, by the type of eruption, and sometimes by skin tests, what sort of eczema it is and then treats it accordingly. What is called "eczema" in infancy is in fact a conglomeration of skin troubles with various causes: atopic dermatitis, seborrheic dermatitis, contact dermatitis, infectious eczematoid dermatitis, nummular eczema, and occasionally *Candida albicans* infection. I shall discuss only seborrheic, contact and atopic dermatitis.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is seen most frequently during the first three months of life. In its uncomplicated form it is almost certainly not caused by allergy, but it is sometimes a precursor of atopic dermatitis. It is probably not the same disease as seborrheic dermatitis in the adult, and "seborrheic dermatitis" is not a good name for it. There is almost always cradle cap, often intertrigo of the armpits, groins and around the umbilicus. It is most often seen in fat babies. The lesions on the body are usually dry and scaly, with fairly sharp margins. If there has been much rubbing, the face may be oozy. It is essentially, however, a scaly and not a vesicular eruption. There is but little itching, which is one good way to differentiate it from atopic dermatitis. The scratch test to egg white is negative; in the presence of a positive egg test it is certain that allergy is in the picture, and that one is dealing with atopic dermatitis, or a mixed seborrheic and atopic dermatitis, which is not uncommon.

The cause of seborrheic dermatitis is obscure—I have always thought that fat in the diet probably had a good deal to do with it. It has been suggested recently[1, 2, 3] that a lack of biotin is the cause, and encourag-

ing results have been reported by the injection or oral administration of this vitamin. So far I have had too little experience with biotin to express any personal opinion about it that would be of any weight.

Treatment is satisfactory. In young babies a low fat, low sugar and high casein diet is almost specific. Such a formula is obtained by the use of partly skimmed milk, water, and the addition of 4 tablespoonfuls of Casec flour to the quart of formula. The rest of the diet can be the same as it would be for any child of the same age. It has been thought in Germany that the addition of liver and of vitamin B complex does good. This is probably so.

For local treatment of the scalp a weak salicylic acid and petrolatum salve applied thickly for several days, and followed by a shampoo, is efficient in getting rid of most of the crusts and scales. This is then followed by the daily application of Pragmatar* ointment diluted one half with petrolatum.

For lesions on the body and face there is nothing better than a crude coal tar ointment or paste.

ATOPIC DERMATITIS

If one believes, as I do, that atopic dermatitis in the infant is caused by allergic sensitivity to specific foods or environmental allergens, it is important to remove these from the diet and environment. Of the environmentals, feathers, dust and wool are the most important; of the foods, egg, wheat and milk. It is probably true that these infants can be treated more intelligently if a few skin tests are done, but if the child is put on a well balanced diet of foods which rarely cause trouble, and local treatment is intelligently carried out, the practical results are likely to be as good as if skin tests are done. The egg white test is particularly valuable in differential diagnosis, and possibly may be also of some prognostic value: a child with a strongly positive egg white test is a highly allergic child, and it has seemed to me that he is more likely to have hay fever or asthma later than a child with a weakly positive or negative egg white test. Skin tests to foods in infancy are usually pretty reliable.

A suitable diet is as follows: Milk or a milk-free food such as Mull-Soy or Sobee. Rice, lamb, string beans, carrot, turnip, squash, apple sauce, Vipenta drops and ascorbic acid. Such a diet is well balanced, and the child can stay on it for a long time.

If there is a positive scratch test to lactalbumin, it is likely that the use of a milk-free diet will do a great deal of good. If the scratch and intracutaneous tests to lactalbumin are both negative, a milk-free diet will probably not accomplish much. However, most babies who have

* Smith, Kline & French. It contains sulfur, salicylic acid and tar.

eczema are treated without doing skin tests, so that a milk-free diet is commonly used according to the method of trial and error, which is justified unless the baby is in a poor state of nutrition or has a tendency to diarrhea, for Mull-Soy and Sobee, although they have been considerably improved in the last three years, even now may cause diarrhea. The trouble is that milk sensitivity and its cure by these foods have been advertised so much that a good many doctors seem to think that almost any skin eruption in infancy is caused by sensitivity to cow's milk, and will be cured by a milk-free diet. This is certainly not so.

Most babies with atopic dermatitis give positive scratch tests to egg white, and are clinically sensitive to it, sometimes violently so. Many believe that this sensitization has taken place in utero. It has been difficult, however, to see how egg sensitivity could have anything to do with the eczema, because eczematous babies do not eat egg. What one often sees is a baby of four or five months who has no demonstrable sensitivity to anything *except* to egg white—the removal of milk or wheat or anything else from the diet does no good whatever, nor can it be demonstrated that environmental allergens are involved. Nothing does any good except local treatment. It is not impossible that in such babies the egg white sensitivity may have to do with the eczema. It has become well known in the last few years that antigen can be retained in the body for a much longer time than had been previously thought possible, and it may well be that the trouble is due to egg antigen which originally reached the child's tissues while he was still in utero. This is analogous to the urticaria which may last for many months after one penicillin injection. This idea is, however, no more than a hypothesis—it is by no means proved.

It is well worth while to try to get at babies who have atopic dermatitis by immunologic methods such as I have discussed, and results are sometimes brilliant. The trouble is that they are not brilliant frequently enough, and often really skillful local treatment does more good than anything else. Most allergists do not pay enough attention to it—they have so much faith in allergy that they think they will usually find the answer by allergic methods, and that anything else is quite secondary. I doubt whether this is so.

Local treatment will not be discussed in detail because the only way that it can be learned is by experience. It is important for allergists and pediatricians to pay more attention to the strictly dermatologic aspects of eczema than they usually do. By this I mean careful observation of the morphology of the eruption, and the use of the proper local treatment for this particular morphology. Only two local medicaments will be discussed: crude coal tar and hydrocortisone.

If there is one thing that everybody dealing with infantile eczema is agreed upon, it is that crude coal tar in some form, when used prop-

erly, is a valuable remedy. I first saw it used when I was a medical student at the Massachusetts General Hospital in 1912—it was introduced there by Dr. Charles J. White just about then. This was 47 years ago—it has stood the test of time. There has been much improvement in the coal tar preparations. It was formerly necessary to have tar pastes and ointments made by a druggist—sometimes they came out well, sometimes not. This is no longer necessary, since some of the large drug houses now turn out very fine tar preparations. The ones I like best are Daxalan and Kolpix ointments, made by the Dome Chemical Company, and Tarquinor, made by Squibb. Daxalan is black and closely resembles Dr. White's original tar paste. Kolpix ointment is made up in a water-soluble base, and has been treated in such a way that it has lost some of its color. Squibb's Tarquinor is also a water-soluble preparation, and in addition to tar it contains the antiseptic Quinolor, which is sometimes a considerable advantage. I also use a great deal a tar paste made very thick with bentonite, which was devised at the Children's Hospital Pharmacy with the valued help of some of the experts at the College of Pharmacy across the street. This preparation contains only a small amount of tar, so that it is not dirty. Its chief virtue is that, owing to its thickness, it stays on the skin well.

Tar and Bentonite Paste

Bentonite, U.S.P.	7.50
Crude coal tar	4.0
(or Liquor carbonis detergens, N.F.)	15.0
Water	15.0
Burrowes Wellcome neobase (or Hydrophilic ointment, U.S.P.)	7.50
Paste zinc oxide, U.S.P.	45.0

Crude coal tar undiluted is not used enough. It is unsurpassed for the treatment of small thick lesions such as occur in nummular eczema.

There can be no doubt that hydrocortisone ointment is a valuable adjunct to treatment. It by no means always does good, however, and is not so valuable as tar for thick sluggish lesions without much active inflammation. I am doubtful whether the newer steroids such as prednisolone and fluorocortisone are any better than the original hydrocortisone for use on the skin. One trouble with the steroid ointments is the same as for any steroid treatment: results are likely to be only temporary. If I had to throw overboard either crude coal tar or steroid ointments, the steroids would go.

In my opinion, contrary to the opinion of some, no steroid ointment should be used when eczema is infected, whether or not an antibiotic has been added to it. It is far better to get rid of the infection first with an antibiotic alone. I have seen two cases in which there was probably a sluggish *Staphylococcus aureus* infection without pustulation, blossom out into extensive pustulation after the use of a combined hydrocortisone and neomycin ointment.

Protection of the skin from outside trauma, so far as it can be done, is of the utmost importance. No skin inflammation can heal when there is continual scratching, picking and rubbing, as there always is with these children. A large amount of what one sees on any child with eczema is what he does to himself. If there is eczema of the wrists, ankles, legs or arms, these parts should be bandaged. There is no other way to protect them, and no matter what choice and expensive salve is used, there will be no improvement as long as the child is continually at work on himself. This is not sufficiently appreciated. There is no use in bandaging with ordinary bandages—they do no good. Over whatever paste or ointment is used there is first put a layer of soft cotton cloth from a sheet, pillow case or old shirt; then over this goes an Ace elastic bandage. The 2-inch width is best. This is kept on 24 hours a day, and is removed only to apply new salve. I always like to see children with arm or leg eczema—results are good because these parts can be bandaged.

Atopic dermatitis in children between the ages of 4 and 12 years is more likely to be due to environmental allergens than to foods, and even in infants this may be so if the trouble has begun not until the second year and has first appeared at the back of the knees and in front of the elbows instead of on the face, where it usually begins in younger infants. The most important environmental allergens are dust, wool and pollen. Dust and pollen probably work by inhalation; wool either by inhalation or contact. Atopic dermatitis due to one of these, or sometimes to all three combined, is far more common than is generally realized. It is pretty hard to avoid dust and pollen, and so the question of hyposensitization sometimes has to be considered. There is much difference of opinion about this, but all are agreed that if it is used, the dosage should be very small, much smaller than is used in treating respiratory allergy. It is worth a trial in severe cases, but in my opinion it does not rank with hyposensitization in hay fever. I have not been able to get the consistently good results that have been reported by some. I have treated 21 cases, mostly with pollen, with satisfactory results in only 9. My present practice is to give the injections intracutaneously, beginning a few weeks before the pollen season, and to use just enough dosage to produce a wheal about as big as a five-cent piece. This amount of reaction is obtained as a rule from the same volume of extract that would be used in doing a skin test, in strengths of 1:10,000 or 1:100,000. I am doubtful whether it is often necessary to use the infinitesimal doses recommended by Rowe, although I have seen a severe exacerbation which took 3 weeks to get rid of, caused by the subcutaneous injection of 0.10 cc. of 1:100,000. It has seemed to me that with the small doses used, frequency of inoculation is desirable, and for this reason some mothers can be taught to do it them-

selves, twice a week. It does not make sense to start the inoculations during the season when eczema is present. If the eczema is being caused by pollen absorbed through the nose and getting into the blood and thence to the skin, it certainly is not reasonable to add more of the same. If inoculations are started when there is no pollen in the air, the question is quite different.

STEROID THERAPY

It has become evident in the last two years that if a child is taking cortisone internally and gets chickenpox or Kaposi's varicelliform eruption or eczema vaccinatum, it may go hard with him, since steroid therapy greatly lowers resistance to these particular viruses, and no antibiotic will protect. This means that now there is little use for steroid therapy in young infants with eczema. It is best not to use it for any child with eczema or asthma, except for possibly short periods in emergency, unless the child has had chickenpox. I do not think it is well to use it for eczematous children when it is likely that chronic *Staphylococcus aureus* infection may be involved in the eczema, as it is in infectious eczematoid dermatitis, atopic erythroderma, and possibly in nummular eczema. It has seemed to me that in these conditions, though temporary results may at times be spectacular, the course of the disease is actually much prolonged. In spite of these restrictions, steroid therapy still has some use in dealing with eczematous children, provided they have had chickenpox, as follows:

1. A severe, acute self-limited contact eruption, such as poison ivy.
2. An infant with a very oozy face, which, owing to rubbing, has been impossible to control with the usual methods of treatment. A few days' treatment with cortisone or Meticorten* will dry it, so that tar paste may be used, which will usually prevent recurrence of the oozing.
3. The next indication is best illustrated by a specific case: a child of 3 years with a severe generalized atopic dermatitis, possibly due to dust. There are 4 children in the family. The mother does the cooking, laundry and housework. The child itches all the time, and is a cranky child anyhow, entirely apart from the itching. He scratches so much that most of the time he is bleeding. He tears off all bandages. He sleeps hardly at all—neither do his parents or his brothers, who are in the same room with him, so that the whole family is in bad shape, and the mother, who is a highly excitable woman anyhow, is about ready for a sanatorium. Something has got to be done to relieve the whole situation, and done quickly. There are only 2 ways of doing it—either hospitalize the child for several weeks or use cortisone. Twenty-six dollars a day for hospitalization is out of the question for this particular family—therefore cortisone is the answer. The boy was kept on it in moderate dosage all winter, he and his family calmed down, and everything was fine. In the spring cortisone was gradually discontinued, and for some strange reason the eczema recurred only a little and has since been kept under reasonably good control with local treatment.†
4. Cortisone or Meticorten is valuable in dealing with eczema due to pollen, inasmuch as to some extent this is a self-limited situation, and the eczema often recedes

* I prefer to call this substance "Meticorten" rather than "prednisone."

† This child had had chickenpox.

fairly well by itself when the pollen season is over. For a severe atopic dermatitis due to pollen the only 2 things that will really relieve an acute situation are to go to some place where there is no pollen or to use steroid therapy. Pollen inoculations begun when the eczema is acute in the pollen season are likely to do more harm than good.

It has seemed to me that 75 mg. of cortisone a day or 20 to 25 mg. of Meticorten is enough for most children with eczema. As soon as the symptoms are controlled the dose is dropped, and is kept at the lowest possible level that will do good. This is often 37.5 to 50 mg. a day of cortisone, 10 to 15 mg. a day of Meticorten. It is unusual for any child with eczema to be kept free from it on the small doses that sometimes suffice for a child with asthma.

CONTACT ECZEMA

Much of the eczema that infants and children have is atopic dermatitis, and in infants, particularly, this is sometimes due to food. The idea is firmly fixed, however, in the minds of many doctors, pediatricians particularly, that just about all eczema in children is caused by food. This is by no means so—contact dermatitis, which has nothing whatever to do with food, is common. Too many children are dieted when the trouble is really due to something which contacts the skin from the outside. I wish to emphasize this particularly, and so will repeat it. Too many children are dieted when the eczema is due to external causes and has nothing to do with the diet.

Contact eczema should be suspected if the eruption appears suddenly on a previously healthy skin, or if it is confined to one portion of the body, with fairly sharp lines of demarcation. This is particularly true if it first appears on the hands, wrists, around the neck or on the limbs. Scratch tests may be negative or positive, and it is by no means uncommon for children to have at the same time contact dermatitis from various external contacts with simple organic or inorganic chemicals in all manner of things which contain them, as well as atopic dermatitis from the ingestion or inhalation of protein food or environmental allergens. The general opinion is that contact dermatitis is a distinct disorder from atopic dermatitis, dependent upon a different mechanism. This is probably right. It has also been thought by many that atopic people are no more likely to have contact dermatitis than are nonatopic people. I doubt whether this is so, and it has seemed to me that children with atopic dermatitis are more likely to have contact eruptions than are normal children.

I have done a good many patch tests on children who had contact eczema, and although there have been a few strongly positive reactions, in general patch tests have been of little help. The reason for this may be that in children a good many contact eruptions are due to primary irritants of no sensitizing power, and relatively little irritating power, so that long-continued contact with the addition of rubbing is necessary before dermatitis is produced. Contact dermatitis is not so common

in infants and children as in adults because they are not exposed to the large number of sensitizing contacts that adults are. I have seen it in children, however, from neomycin, Orlon, nylon, perfumery, primrose, mulberry leaves, dyes, furniture polish, turpentine, tincture of green soap, mercury, tar, sulfur, Sopronol, patent hair shampoo, hair tonic and creosote. But such things are not the things which *commonly* cause contact eruptions in children.

A few months ago I went over the records of 200 consecutive cases of eczema seen in my office. The diagnosis of contact eczema, rightly or wrongly, was made in 53. The cause was determined with reasonable accuracy in 31, probably in 18, and not at all in 4. These causes were as follows:

Wool	16	Dye	2
Diapers (not $N.H_3$)	8	Rubber	1
Diapers ($N.H_3$)	4	Nail polish	1
Plastics	4	Shoe lining	1
Corduroy pants	4	Underclothes	4
		Ivy	2

It will be seen that if the diapers and shoes are included as clothes, 40 out of the 53 cases were probably caused by something to do with the clothes. Such a high percentage (74 per cent) would not be found in adults. Wool is the most common cause. Eczema due to wool occurs in children particularly around the neck, and on the wrists, forearms and ankles. Scratch tests to wool in these patients are rarely positive; positive intracutaneous and patch tests are more common. Although a high degree of allergy to wool can occur, so that eczema or urticaria is produced by only slight contact, it seems likely that a large part of the eczema due to wool is caused by its action as a primary irritant rather than as an allergen. As an allergen, it is of considerable interest, for it can cause contact dermatitis by external contact, with epidermal sensitization and positive patch tests, or atopic dermatitis by inhalation, with dermal sensitization and positive scratch or intracutaneous tests.

I have used hyposensitization to wool in three patients, with pretty good results. The top dosage was 0.20 cc. of 1:10,000. In one patient, after a small dose of 1:1000, there was a flare-up of the already existing eczema within 24 hours, and a papular eruption all over the body somewhat resembling an "id" reaction. Dosage must be kept small.

Children frequently come into contact with plastics and synthetic fibers. These are complicated chemically, and may contain primary irritants as well as many sensitizing substances. Bibs, toys, diaper and mattress covers should be under suspicion. I have seen four cases of contact eczema due to Orlon, one to nylon. Most sweaters that young females wear now are made of Orlon. They almost always wear the sweater over bare arms, and if one sees a child, usually a female, with

a subacute dermatitis of the forearms, lower third of the upper arms, and wrists, with a fairly sharp line of demarcation where the upper arm has been protected by a quarter-sleeved waist or undergarment, and she has been wearing an Orlon sweater, there is a fair chance that the sweater is the cause of the eczema.

Cotton fiber itself is never allergenic. However, most cotton garments have been treated with chemicals for various purposes. Some of these are starches, alkalies, synthetic resins, which may contain free formaldehyde, lubricants, wetting agents or bleaches. These may cause trouble.

In my experience contact eczema in children due to soap is rare. I have seen one case due to the oil of lavender in tincture of green soap —none that I thought was caused by any other soap.

It must be emphasized that eczema, particularly atopic dermatitis, is by no means well understood, and that there is much difference of opinion about it. I would have no reader believe that it is so simple as might appear from the foregoing brief discussion of practical management.

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INFECTIOUS ECZEMAS IN CHILDREN

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Infection plays such a great part in many eczemas that they are called infectious or microbic eczemas. In some instances bacterial infection and sensitization to bacteria are primary causes; in others secondary infection is superimposed on an existing eczema. In others the relationship between infection and eczemas is not fully understood, as in the so-called nummular eczema. Practically, the difference between various forms often is not too great. Secondary invaders may take over the field so completely that the problem confronting the physician is the same as in primary infectious eczema.

In their classic manifestations the more common forms of infectious eczemas correspond to fairly well defined entities. But often enough we are dealing with atypical forms or transitional cases which cannot always be properly labeled. This, however, is not of too great practical importance, since the treatment of the various forms of infectious eczema is very similar.

TABLE 8. *Classification of Infectious Eczemas*

I.	Infected eczemas
	A. Infected infantile eczema
	Kaposi's varicelliform eruption (eczema herpeticum)
	Eczema vaccinatum
	B. Infected juvenile eczema
II.	Infectious eczematoid dermatitis (bacterial eczemas)
	A. Infectious eczemas of the ears and surrounding area
	B. Infectious eczema of hands and feet
III.	Intertrigo
IV.	Nummular eczema

There is considerable difference of opinion, and confusion, as to what is an infectious eczema. In this article I shall discuss those eczemas

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in which microbial infection and sensitization to microbes or their products play a significant part, for the simple reason that recognition of the infectious component is important for their proper management.

The general term "infectious" or "microbial eczema" denotes that all kinds of microorganisms may be the cause. Bacteria rank first; fungi are next, though much less important, and other parasites, such as mites, run a poor third. Viruses also have to be considered in secondary infection. Classification as "infectious" eczemas refers to their microbic nature; it does not necessarily imply that these eczemas are contagious, although some are.

Primary infectious eczemas are relatively rare in infants. In babies they are seen mostly in the form of intertrigo; beyond infancy the typical picture of infectious eczematoid dermatitis is more common, and nummular eczema occurs. Secondarily infected eczemas, however, are common from early infancy through childhood, usually as infected atopic dermatitis.

ETIOLOGY AND PATHOGENESIS

The role of common pyogenic organisms such as staphylococci and streptococci in the causation of eczema had been recognized for a long time, especially by French dermatologists. Later on, when the role of allergic sensitization was emphasized, the infectious side became neglected or was frankly denied. The situation can be easily understood. Bacteria were still found abundantly in eczemas; but they were considered essentially contaminants. During the last 15 years the pendulum has swung back again, and infectious eczemas have staged a comeback through the back door of bacterial sensitization. The importance of bacterial factors in eczemas has been stressed by several authors.[2, 6–10] The causative organisms in infectious eczemas are usually *Micrococcus pyogenes* (*Staphylococcus aureus*) and *Streptococcus haemolyticus*. However, *Escherichia coli*, the Proteus, the Pyocyaneus and the diphtheria bacillus, and other bacteria may also cause infectious eczemas.

The bacteriologic proof of infectious eczemas is difficult because the most common offenders, staphylococci and streptococci, are also found on normal skin, and often in many nonbacterial dermatoses. Therefore the demonstration of these microorganisms is not necessarily proof of their causative action. In spite of this there is now good evidence for the bacterial origin of infectious eczemas. Storck[8] showed that there is a great quantitative difference in the microbial content of certain eczemas. Staphylococci were especially abundant in bacterial eczemas (or what has been called the acute phase of seborrheic dermatitis) and nummular eczemas. Fowle and Rice[4] confirmed these findings in nummular eczemas. The etiologic role of bacteria was furthermore sug-

gested by a parallelism between regression of the eczematous lesions and reduction of their bacterial content which Storck observed in penicillin-treated bacterial eczemas. This author was also able to reproduce eczematous lesions in some of his patients by inoculating normal skin with the patient's own bacteria or with material from his eczematous plaques.

Still more significant are Storck's studies about allergic sensitization to bacteria and their products. Scratch-patch tests with the microbes isolated from the eczematous patches produced eczematous responses in most instances. *Staphylococcus aureus* gave positive reactions in 68 per cent, *Streptococcus haemolyticus* in 24 per cent, and *E. coli* in 11 per cent. Some patients were sensitized to several bacteria. Ulbricht[10] studied bacterial sensitization of infectious and nummular eczemas by means of scratch-patch tests with bacterial infiltrates; he confirmed the findings of Storck and concluded that the nummular eczema-like lesions so often secondary to infectious eczema are a sensitization phenomenon due to bacterial toxins. The specificity at times was so great that patients reacted only to extracts from their own bacteria.

Much of the pathogenesis is not clear. Storck believes that the development and spreading of microbic eczemas can best be understood by the presence and multiplication of great numbers of antigenic bacteria after the epithelium has been damaged by conditions conducive to intensive microbial growth, for instance following trauma, pyodermas, toxic effects or contact dermatitis. Lesions of nummular eczema can be provoked by a distant, noncontiguous focus. Internal foci of infection also may be factors in bacterial eczemas. The beneficial effect of elimination of foci of infection, and the temporary aggravation seen at times immediately after removal of infected teeth or tonsils leave little doubt about this relationship.

Mechanisms of Infectious Eczemas

In a general way I may say that an infectious eczema is due to a combination of an infection and an eczema. Such an association may occur in different ways.

1. Infection of the skin may lead to an eczematous sensitization to the causative organisms. In bacterial infections the resulting eczema corresponds to what is known as infectious eczematoid dermatitis or bacterial eczema.

2. An infectious process of the skin may become complicated by a dermatitis of a different nature, for instance a contact dermatitis. This may produce a clinical picture undistinguishable from infectious eczematoid dermatitis.

3. An eczematous dermatitis may become complicated by secondary infection; the resulting eczema is here called an infected eczema. Often the term "acute seborrheic dermatitis" is applied to such eczemas.

4. Infection and infectious sensitization of the skin seem to be associated in some way with other forms of eczema, notably some cases of nummular eczema.

All forms of infectious eczema may be complicated by various types of sensitization such as bacterial, contact or autosensitization. This may lead to secondary allergic eruptions, which are known as "id"-like eruptions, "allergids," "microbids," "eczematids."

Table 9 lists the sources of local or focal infections.

TABLE 9. *Source of Infection*

LOCAL INFECTION (SKIN)	FOCAL INFECTION
Furuncle	Teeth
Draining abscess	Tonsils, sinus
Draining ear	Gallbladder
Impetigo	Respiratory tract
Intertrigo	Gastrointestinal tract
Paronychia	Cervix, prostate
Trichophytosis	Monilia infection of vagina
Moniliasis	Monilia in intestines

In children impetigo, furuncles, draining ears, fissures below the ear lobes and intertrigo seem the most common sites of local infection, whereas tonsils, teeth and sinuses appear most significant for focal infection.

DIAGNOSIS OF INFECTIOUS ECZEMAS

The clinical picture, the history, bacteriologic studies, skin tests and the finding of a focus of infection all may contribute to establish the diagnosis.

Often the clinical signs of infection are obvious; it is easy to recognize such frank secondary infection as an impetigo, folliculitis or paronychia. But once eczematous sensitivity to the microbes has developed, all we see is usually just a dermatitis, and one may only suspect the infectious factor. One of the telling signs may be a sharp roundish or polycyclic border.

The history, important in all forms of eczema, often will reveal the infectious source, and also other significant data, such as an atopic background.

The bacteriologic diagnosis is difficult. The demonstration of staphylococci or streptococci by itself does not prove anything, since they are often found in most eczemas. Abundance of these microbes, however,

is suggestive. Positive skin tests with antigens from these cocci also are not convincing proof, because many children and infants give positive delayed reactions to them apparently not connected with any skin disease. These tests have little practical value. However, a severe reaction, especially connected with flare-ups of the eczema, is suggestive, not only of infectious eczema, but also of an underlying focal infection.

CLINICAL MANIFESTATIONS OF INFECTIOUS ECZEMAS

Infected Infantile Eczema

The most common form of widespread infantile eczema is *atopic dermatitis*. It is prone to secondary infection. Scratching obviously is a factor, but not the only one. There are also seasonal influences, since severe secondary infection is especially frequent between January and April. Often the signs of infection are obvious in the form of pustules or impetigo-like crusted lesions. The whole eczema may become infected, resulting in a severely ill infant with a temperature of 101° to 103° F. Usually the infection is less severe with parts of the eczema covered with pustules, and other parts showing no signs of infection. These cases are easily recognized as infected eczemas. One may find all transitions from a typical infantile eczema with discrete pustules (Fig. 12) to cases in which the eczema is completely masked by the secondary infection (Fig. 13).

The situation is more difficult when eczematous sensitization to bacteria exists. Then secondary infection often manifests itself only as an aggravation of the eczema, especially in the form of an acute, weeping dermatitis, simulating a contact dermatitis. Sometimes round and circinate lesions suggest the infectious factor. In these instances the infec-

Fig. 12. Infantile atopic dermatitis with moderate secondary infection, marked by crusted lesions especially on the forehead.

Fig. 13. Severely infected atopic infantile eczema. On the left cheek the infection has superseded the eczema so completely that the picture resembles an infectious eczematoid dermatitis.

tious part is often overlooked by the physician. In spite of various local medications these eczemas frequently fail to improve until the infectious nature of the dermatitis is recognized. Parenteral antibiotics may cause dramatic improvement in these cases.

KAPOSI'S VARICELLIFORM ERUPTION (ECZEMA HERPETICUM). I should mention here that peculiar severe secondary infection of infantile atopic dermatitis which is called Kaposi's varicelliform eruption or, for short, Kaposi's eruption. This is a generalized infection with the virus of herpes simplex. Severe cases are alarming. The infants are very sick, and have fever between 104° and 105° F. The eruption is characteristic, consisting of umbilicated pustules and papules resembling vaccinia. Those who have seen this picture can recognize it immediately for what it is; the uninitiated usually considers it a pyogenic infection. Kaposi's eruption is a serious disease. Fortunately it is rare; the mortality rate formerly was about 50 per cent. Treatment with antibiotics has improved the prognosis, although these drugs have no known effect on the herpetic infection. These children also may have an overwhelming secondary bacterial infection, and it is likely that antibiotics help by checking the pyogenic invasion.

The infants require hospitalization, careful, mild antiseptic local treatment, and the general pediatric care necessary for severely ill infants. Regardless of the treatment, the high fever usually lasts for about four to five days. It is during that time that the physician and parents may get panicky; there is usually nothing gained from a change of the antibiotic or sulfonamide, but one should be sure that the secondary invaders are sensitive to the drug used. Gamma globulin should be given in severe cases. As in other persistent infections, one may be tempted to try a combination of corticosteroids and antibiotics. In view

of the disastrous results cortisone and its derivatives may have on herpetic infections, these drugs should not be used in Kaposi's eruption. If the baby does not succumb during the first four or five days—and most infants now survive with proper treatment and good nursing care—there is rapid recovery, usually with little scarring.

ECZEMA VACCINATUM. Another viral complication of atopic infantile dermatitis is eczema vaccinatum. Clinically it may look identical to Kaposi's eruption, because the typical lesion is a vaccinia-like pustule. However, in eczema vaccinatum the cause is the vaccinia virus, occasionally due to vaccination of an eczematous baby, but usually transmitted to the infant from a freshly vaccinated sibling. The treatment is the same as in Kaposi's eruption. It is wise to warn mothers with eczematous children not to have them, or other members of the family, vaccinated until the eczema has completely cleared.

Infected Juvenile Eczema

Atopic dermatitis in older children often becomes secondarily infected. The infection may be confined to residual patches of atopic dermatitis, especially on the wrists. In infected eczemas of older children one must search for underlying conditions, for instance scabies or lichen urticatus. Secondary infection of an eczema of the buttocks and legs often points to pinworm infestation.

Infectious Eczematoid Dermatitis (Bacterial Eczemas)

INFECTIOUS ECZEMAS OF THE EARS AND SURROUNDING AREA. Engman originally coined the term "infectious eczematoid dermatitis" to describe acute weeping eczemas occurring around the sites of chronic infections, such as a running ear, a draining sinus, an infected wound. The designation now is used in a wider sense covering all eczemas of bacterial origin. The original lesion may also be a pyoderma such as an impetigo, or an infected patch of eczema. The ensuing dermatitis may be acute and weeping, or vesicular, or erythematous and scaly; often it is a chronic, crusted, sharply outlined dermatitis, surrounded by satellites. The most common site in children is the ear. Repeated attacks may follow fissures under the ear lobes in infants. In older children it often is secondary to a mild seborrheic dermatitis behind the ears* (Fig. 14) or to "itchy ears."

These bacterial eczemas are persistent and recurrent, and often difficult to treat. The acute attack may easily be brought under control by internally given antibiotics and proper topical treatment (this will be

* Many infectious eczemas subsequent to seborrheic dermatitis are often called "acute seborrheic dermatitis" or "eczematous seborrheic dermatitis."

Fig. 14. Infectious eczema of the ear, secondary to mild seborrheic dermatitis.

discussed under Treatment of Infectious Eczemas*). The parents and the physician often seem satisfied with such a result, but I am not. Flare-ups and recurrences are the rule. Therefore these eczemas need a more thorough approach. Recurrent infectious eczemas of the ears are often found in atopic children. The remaining underlying dermatitis should be treated until cleared. If I cannot find any other cause for the recurrence, I continue with prophylactic treatment of the area by applying for many weeks, or even longer, an ointment made up of equal parts of erythromycin ointment and a cream containing 0.5 per cent hydrocortisone. If it is applied sparingly twice a day, and later on just at bedtime, the expense is negligible; since erythromycin is the least sensitizing of all topical antibiotics (I have never seen contact sensitivity to it), one need not fear sensitization by its prolonged use. At times other underlying factors can be found. Secondary anemia may be present, especially in patients with seborrheic dermatitis.

More important, in my opinion, is the role of focal infection; in children the focus is usually the tonsils, the sinuses, less often decaying deciduous teeth. Such focal infection at times appears also responsible for recurrent bouts of secondary infection in atopic dermatitis. Whatever the relationship between focal infection and recurring bacterial eczemas may be, I have seen great and lasting benefits follow the removal of focal infections too often to doubt the etiologic connection. I am fully aware that many physicians will disagree with me. There are many who fell "hook, line and sinker" for the theory of focal infection

* To avoid repetition, those methods of treatment which are applicable to all forms of infectious eczemas will be discussed in a separate section, whereas specific measures will be described with the individual entities.

many years ago; they were disappointed and now refuse to view this matter in its proper light. During the heyday of focal infection I too was skeptical, but since then I have learned, like others, that focal infection often is responsible for the maintenance of bacterial eczemas.[3] Naturally a patient may have independently a bacterial eczema and a focus of infection. One can never promise that removal or sanitation of the focal infection will benefit the infectious eczema, and I so inform the parents. The approach is easy when there is gross infection of the tonsils with recurrent attacks of tonsillitis, or outspoken sinus disease, because these conditions should be corrected anyway. But with only moderately infected tonsils and no history of tonsillitis the problem is more difficult. In these cases you cannot expect too much help from the otolaryngologist. All he will tell you is that the tonsils are somewhat infected and may or may not be a focus. In these instances I prefer to wait and treat locally and with internal antibiotics. But if recurrences persist, I suggest removal of the tonsils, and often enough only tonsillectomy will reveal severe chronic tonsillar infection.

In cases of recurring bacterial eczema of the ears with no obvious focus of infection I have tried desensitization with bacterial vaccines (see under Treatment of Infectious Eczemas).

Infectious Eczema of Hands and Feet. It is a matter of taste whether one wants to discuss these eczemas with infectious eczematoid dermatitis or separately. In my experience they usually are secondary to a pre-existing infection or eczema. In previous years, when scabies was a common disease, infectious eczemas of the hands often were a prominent sign, requiring treatment even after the itch had been cured. Nowadays most cases are secondary to pyodermas or atopic dermatitis or occur in atopic persons. The following cases are representative.

Case I. A girl had suffered from infantile eczema (a combination of atopic and seborrheic dermatitis) at the age of 7 months. She had had recurrent attacks of mild atopic dermatitis since, involving mostly the antecubital areas, hands and feet, usually worse in winter time. At the age of 11 years an acute weeping dermatitis appeared on the hands, which had not responded to previous treatment. The eczema was considered an acute infectious dermatitis. At that time the other areas of eczema did not show signs of infection. The patient improved rapidly after the internal use of erythromycin and proper topical treatment. Nine months later the patient returned with a recurrence of the acute infectious eczema. This time the infection involved the hands as well as the toes, but not the mild atopic dermatitis present in the antecubital areas. Again there was a prompt response to the same treatment.

Case II. This case illustrates a more chronic form of infectious eczema of the hands. A boy was seen at the age of 11 months because of a diaper rash and seborrheic dermatitis. At the age of 8 years he had a typical atopic dermatitis of the arms and ankles. One year later he presented a sharply outlined eczematoid dermatitis of several fingers of both hands, apparently a secondary infectious eczema (Fig. 15). The occurrence of an infectious eczema (intertrigo) during the first year, and later on the appearance of a secondary infection of an atopic eczema, probably is not a coincidence; it is likely that some people are more prone than others to have this form of dermatitis.

Fig. 15. Infectious eczema of fingers secondary to atopic dermatitis in a boy 9 years of age.

The so-called *idlike eruptions*, also termed *microbids* or *allergids*, are found far less frequently in infectious eczemas in children than in adults. They consist of scattered small eczematous lesions, mostly on arms and legs. They are due to hematogenous spread of bacterial toxins into a sensitized skin.

Intertrigo

Intertrigo is a weeping, acutely irritated dermatitis of the folds of the neck, axillae, groins and antecubital and popliteal spaces; usually it is sharply outlined (Fig. 16). It is an infectious process due to bacteria, especially staphylococci or streptococci, or Monilia (*Candida albicans*). A major factor in intertrigo is the maceration of the skin of predisposed children due to accumulation of sweat in poorly ventilated body folds. Often these are overweight children with deep folds in the neck causing a persistent intertrigo in this region. In the anal folds and groins maceration may be due to urine-soaked diapers. Many cases of "diaper rash" are essentially intertrigo. Secondary eczematous changes may occur, and the intertriginous lesions may spread beyond the folds. At times intertrigo is associated with an infectious eczema elsewhere, as in the following case.

Case III. An infant 8 months of age presented a typical intertrigo of the groin, sharply outlined (see Fig. 15). Cultures showed staphylococci. Skin tests showed good delayed reactions to staphylococcal and streptococcal vaccines. The infant also suffered from an infectious eczema of the right ear lobe and around it.

Such cases suggest that intertrigo may be properly grouped together with the infectious eczemas, although intertrigo probably starts as an infection, and bacterial or monilial sensitivity of the skin follows later.

Treatment in mild cases is simple. Antiseptic drying powders such as

Desenex or Timofax may suffice with proper cleanliness. In more pronounced cases the measures recommended for the treatment for acute infectious eczemas may do the trick. Often, however, intertrigo in children is very resistant. The following regimen has helped my patients in such cases. The skin of the involved folds is gently cleansed of debris and remnants of medication with wet compresses, then well dried. One per cent aqueous gentian violet is applied once or twice a day, and allowed to dry. If possible, the skin is exposed for 10 to 15 minutes to the drying warmth of an ordinary light bulb. One must be careful not to burn the skin. Afterwards a drying antiseptic lotion such as hexachlorophene zinc oil or, in the less acute stage, a hexachlorophene ichthyol paste is applied, and gauze strips are placed in the folds to prevent further maceration. Ointments are best avoided in the acute stage because they tend to increase the maceration. In the more chronic eczematous stage 2 per cent Vioform in zinc oxide ointment and especially Vioform hydrocortisone lotion are helpful. In resistant cases Arning's tincture is applied once a day, ahead of the other medications:

Anthrarobin* 1.2
Ichthyol 1.2
Ether
Alcohol, āā, q.s. 60.0

Because of its alcohol content, this tincture should not be applied to fissures and open sores, since it will cause pain.

Silicone-containing preparations, such as Pro-Derma and Silicote, are often helpful in preventing recurrences. They should be applied only after the intertrigo has subsided.

General measures are important. The mothers are instructed to ob-

* Available through Clinic Pharmacy, Marshfield, Wis.

Fig. 16. Intertrigo of groin (cultures: staphylococci) in a child that also suffered from an infectious eczema of the right ear.

serve strictest cleanliness. In babies diapers must be changed frequently. In severe cases it is best to keep the infants in their crib with only light covering and loose diapers. Rubber or plastic pants are definitely forbidden. This is easier said than done, because many mothers are reluctant to do without these safeguards when the baby is taken out. But it is better to risk a little "accident" than to cause continuous flare-ups. Weight should be controlled, and underlying deficiencies, such as anemia, should be corrected. The urine should be examined. I have never seen diabetes with intertrigo in children, although this association is not infrequent in adults. Routinely, I give these children large amounts of vitamin B, 15 to 25 drops of Multi-Beta 3 times a day. Even so, treatment at home will sometimes fail. Then it is time to hospitalize the infants. I do not change my regimen at the hospital; strangely enough, exactly the same measures which the mother carried out at home without success (or was supposed to carry out) will do the trick at the hospital.

NUMMULAR ECZEMA

There is a form of eczema which occurs essentially in round or oval vesicular patches, most often on the extensor surfaces of the extremities.

Fig. 17. Patchy lesions in infantile atopic dermatitis (sometimes classified with nummular eczema).

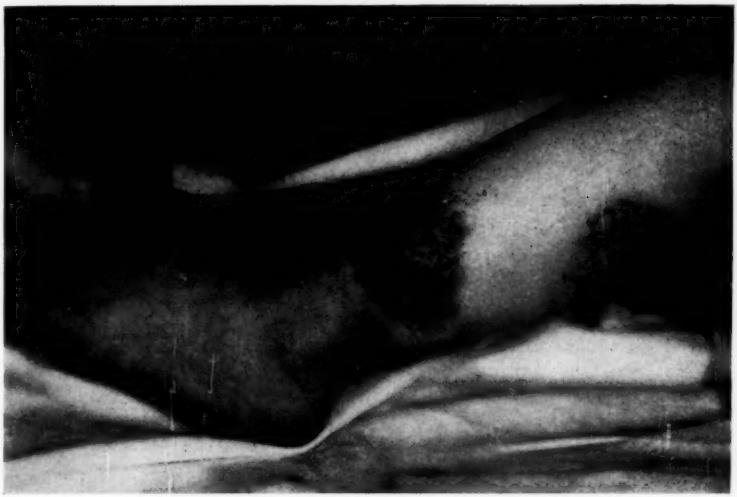

Fig. 18. Nummular eczema of leg in boy 2 years of age.

Because the lesions are round, this eczema is generally called nummular (coin-like) eczema. It is essentially a morphologic entity; it may well be a clinical manifestation of different causes. Sometimes we have sharply outlined, discrete patches; in other instances more irregular groups of vesicles are formed which may coalesce to large plaques. The lesions often regress, and again flare or recur simultaneously, indicating that they are maintained by some internal mechanism. They may persist for many weeks and months or longer.

Nummular eczema in infants and children is rare. It is true that at times numerous round, infiltrated patches of eczema are seen in children with severe atopic dermatitis (see Fig. 17). If one includes these cases under the term "nummular eczema," as Hill[5] does, then it would not be rare. But like most dermatologists, I consider this particular clinical picture just a variant of atopic dermatitis, because it has no resemblance to what is called nummular eczema in adults. This view, of course, is arbitrary; Hill has good reasons to call attention to this particular form of atopic dermatitis because it has its own characteristics and usually is rather intractable.

But there are cases of nummular eczema in children which correspond to the same entity in adults. I have seen a few, most of them in children who previously had atopic dermatitis. The following case is an example.

CASE IV. A child, 2 years of age, had suffered from an eczema of the face and the ears which began when he was 3 months old and lasted about 1 year. About 3 months later, after the infantile eczema had cleared, a different form of eczema appeared on

the boy's legs, which presented the typical picture of nummular eczema (Fig. 18). Routine scratch tests were negative, but there were severe delayed reactions to staphylococcal and streptococcal vaccines. The eczema cleared up within a year with topical treatment. For the next 10 years the boy had no more skin trouble, except for small transient eczematous spots when he ate chocolate.

The cause of nummular eczema is not definitely established. I have previously cited the evidence that bacterial infection and sensitization to bacteria or their products play a significant role in certain cases. The beneficial effect of internal antibiotics supports this viewpoint. I believe with Cope[1] that many cases of nummular eczema are infectious eczemas occurring in atopic persons.

In the *treatment* of nummular eczema coal tar is the most effective topical remedy. I use it as a paste or a lotion (see Treatment of Infectious Eczemas); Vioform often seems helpful and can be combined with the tar. The addition of hydrocortisone appears promising, especially in less acute cases. In resistant cases focal infection is searched for and, if found, eliminated. Internal antibiotics are beneficial.

As supportive measures I prescribe large amounts of vitamin B; in case of dry skin, vitamin A. When indicated, allergic management of an accompanying atopic dermatitis should be instituted, although it does not seem to affect particularly the nummular eczema.

TREATMENT OF INFECTIOUS ECZEMAS

It is important to evaluate the case. In some instances the infection seems to be the main factor, and just the topical application of an anti-

Fig. 19. *A*, Infected infantile eczema. *B*, Same child after antibacterial treatment.

bacterial preparation is all that may be needed (see Fig. 19). In other cases matters are complicated, and several avenues of approach have to be used at the same time.

The following principles govern the treatment of bacterial eczemas.

Local Treatment

Local treatment of infectious eczema consists essentially in a combination of anti-infectious and antieczematous preparations. We must first take care of the infection and acute inflammation, and then treat the underlying or accompanying eczema. Treatment must distinguish between the acute, the subacute and the chronic stages.

Acute Stage. "Wet treatment" in the form of continuous wet compresses relieves any acute inflammation; but such treatment, if properly carried out, requires too much nursing care or is too time consuming at home to be used regularly. Therefore, apart from those exceptional cases which seem to tolerate nothing but wet compresses, I use a combination of "wet" and "dry" treatment, even in the acute phases of eczemas. In infectious eczemas of children compresses with potassium permanganate in a 1:9000 dilution are applied for 15 to 20 minutes, 2 to 4 times a day. My patients and I prefer hot compresses, which in most instances relieve the itching and inflammation more quickly than cold packs. The compresses are applied with several layers of gauze and without an impermeable covering. After the infection has subsided, or when there are objections to the staining potassium permanganate, I use Burow's solution in the form of Domeboro packs, 1 packet dissolved in 1 quart of water; for feet and hands, soaks of 10 to 15 minutes' duration are usually more effective and more easily applied. Even in the acute phase the compresses or soaks are alternated with the "dry treatment."

For "dry treatment" calamine liniment or a "zinc oil" with an antiseptic is used. My preferred antiseptics are hexachlorophene or Rivanol.* The formulas are as follows:

10% hexachlorophene in corn oil (Ar-Ex Cosmetics, Chicago, Ill.)	12.0
(or Rivanol	1.2)
Calamine liniment, q.s.	120.0

or

10% hexachlorophene in corn oil	12.0
(or Rivanol	1.2)
Ichthyol	2.4
Zinc oxide	48.0 gm.
Corn oil, q.s.	120.0 cc.

Be sure the oil is added in such a quantity as to make the volume of the mixture total 120.0 cc. Then it will be a heavy, oily suspension. This is applied three times a day, with or without bandages. If the skin

* Rivanol can be obtained from the Clinic Pharmacy, Marshfield, Wis.

becomes too dry, alternate with an ointment consisting of equal parts of yellow petrolatum and cold cream without rose water. If the infection is stubborn and the skin irritable, a 1 per cent aqueous gentian violet solution is often effective in acute infectious eczemas, but this is also messy.

Subacute Stage. The same calamine liniment and "zinc oil" may be used first. Antibiotic ointments are helpful; I use those containing erythromycin (Ilotycin ointment) or neomycin and/or bacitracin and polymyxin such as Neosporin ointment or Myciguent. Two per cent Vioform in yellow petrolatum or in a cream base helps against both infection and eczema. The effect of these antibacterial agents may be enhanced by combining them with hydrocortisone or one of its newer derivatives, e.g., 1 per cent Neo-Cortef ointment, Hydroderm, Neo-Cort-Dome, Terra-Cortril, Neo-Magna-Cort, Cortisporin, or an ointment composed of equal parts of Ilotycin ointment and 1 per cent Cort-Dome cream. When a paste is indicated, I use the following:

10% hexachlorophene in corn oil	3.0
Ichthyol	0.6
Corn oil	3.0
Lassar's paste, q.s.	30.0

This is applied once a day with a bandage or twice or three times daily without bandaging.

Chronic Stage. In this stage the eczema is more important than the infection, and coal tar is the favorite medication. Crude coal tar is still unsurpassed, and because of its superior effect parents usually do not object to its messiness. I use 3 per cent coal tar in zinc oxide ointment; when a lotion is indicated, crude coal tar can be incorporated into a shake lotion, but the preparation of such lotions is somewhat complicated. It is simpler to add 3 per cent liquor carbonis detergens to a zinc lotion of the following composition:

Ichthyol	2.4
Zinc oxide, Talcum, āā	25.0
Glycerin, Alcohol, Water, āā, q.s.	120.0

If the parents object to the messiness of crude coal tar, liquor carbonis detergens is a fair substitute; it may be applied in 3 to 5 per cent strength in zinc oxide ointment or, when the skin is dry, in yellow petrolatum. For those who prefer a less greasy preparation I use the following:

10% hexachlorophene (in corn oil)	3.0
Liquor carbonis detergens	1.0
Acid mantle cream, q.s.	30.0

Coal tar is especially helpful in nummular eczemas. Since tar may cause follicular infection, and since we are dealing with infectious

eczemas anyway, I always add an antibacterial drug to the tar ointment (1 per cent Rivanol, 1 per cent hexachlorophene, 2 per cent Vioform or 3 per cent ammoniated mercury, or I mix 1 part of a neomycin-containing ointment with 2 parts of the tar ointment). The following ointment seems to work well in chronic and subacute infectious eczemas of the hands:

Vioform	0.6
Dermaftan	1.5
Corn oil	3.0
Lassar's paste and yellow petrolatum, āā, q.s.	30.0

A few general remarks may be helpful: The medication must be appropriate for the stage of the dermatitis. Do not use a strong ointment during the acute phase; do not apply a washable cream on a weeping dermatitis. Do not overtreat. If the treatment is not immediately successful, do not change constantly to different medications. Try to stick to a few tested preparations which have a low sensitizing index. Apply your antiseptic ointment only to the areas where there is actual infection. In generalized eruptions the "id"-like rash accompanying the infectious eczema is purely allergic and not infectious. This eruption usually requires only mild local treatment.

Equally important as the choice of the medication is its proper application. Wet compresses that are allowed to dry out and stick to the eczema are of no help. The skin must be properly cleansed, debris and crusts must be removed, and pustules evacuated before the medicament is applied. But too thorough cleansing also must be avoided, so as not to interfere with regeneration of the skin. When the skin is dry, the cleansing may be carried out with an oil-soaked sponge; to remove remnants of a sticky ointment, a mild soap solution of pHisohex may be used. There is no need to remove all the remants of the old ointment unless there is infection beneath. It is necessary to apply enough of the medication so that there is some left on the skin when the bandages are removed. Change of bandaging depends on the stage and on the patient's comfort. In the more acute stage bandages may have to be changed two or three times a day; later on they may be left in place for two or even three days.

Contrary to general opinion, mild soaps and short baths are often tolerated by eczematous children. Although most infectious eczemas are not very contagious, it is well to isolate from their siblings those infants and children who show outspoken signs of infection, especially impetigo. When hospitalized, all children with infectious eczema or infected eczemas should be isolated until the infection is under control.

Systemic Treatment

Unless there is severe infection or a widespread eruption, I like to withhold systemic antibiotics and watch the effect of local treatment. If this

is not very helpful, antibiotics should be given internally. In primary infectious eczemas as well as in secondarily infected eczemas I usually prefer the broad-spectrum antibiotics such as tetracycline, Terramycin and erythromycin to penicillin, because the main causative bacteria are often penicillin-resistant* staphylococci.

Treatment of Contributing or Underlying Conditions

The correction of contributing or underlying factors is important. A thorough allergic investigation for contact as well as food and environmental allergies and management from this angle may be necessary in resistant and recurrent cases, encountered in atopic children. Anemia and nutritional deficiencies may be contributing factors. I routinely prescribe, in addition to the regular vitamin mixtures, large amounts of vitamin B complex in all forms of infantile eczema; usually Multi-Beta, 15 to 25 drops 3 times a day; however, I have not been impressed by the addition of vitamin B_{12}, and I do not believe that it is worth the additional expense in eczemas. In case of an underlying dry skin I add vitamin A, 50,000 to 100,000 units daily, according to age, especially during the cold winter months.

Foci of Infection. Before attempting to remove foci of infection in bacterial eczema, one must wait until the eczema is under control. The patient should receive adequate amounts of penicillin or some other antibiotic at least 48 hours before the removal of the focus, and for 3 days afterwards, depending on the severity of the infection.

Desensitization. Desensitization in infectious eczema should be reserved for recalcitrant cases; it is not a routine method. It seems to me most effective in constantly recurrent infectious eczemas of the ears in atopic children. It is a tedious procedure and difficult to evaluate. However, instances in which the bacterial eczema cleared after desensitization and recurred only several months after desensitization had been stopped are suggestive that desensitization works in selected cases of bacterial eczemas. The efficacy of this treatment is also indicated by the flare-ups caused by too large doses. These reactions usually occur within 24 hours after the injection. In this case the dose must be reduced. For routine desensitization in bacterial eczemas I use a mixture of staphylococcal and streptococcal antigens. The starting dose depends on the results of the skin tests. With severe delayed reactions I begin with a 1:1 million dilution, or less, otherwise with a 1:100,000 concentration, building up in the usual way, but not beyond a 1:10 dilution of the commercial vaccines. If the patient encounters frequent reactions, I try intradermal injections of 0.05 cc. of a 1:100,000 dilution every fifth day,

* Oral therapy with the tetracyclines may be followed by staphylococcal enterocolitis. I have hardly ever encountered this complication, but one must be alert to the possibility and promptly stop the tetracycline and institute symptomatic treatment.

without attempting to increase the dose. When children object too strongly to injections, or when injections are too inconvenient, I have tried oral desensitization. It seems to work occasionally; certainly this method has caused aggravations in some instances. However, I have not had enough experience with this technique to commit myself definitely.

PSYCHOSOMATIC FACTORS. In infectious eczemas in children such factors are encountered almost exclusively in cases combined with, or superimposed on, atopic eczemas. But in almost all cases the parents require supportive psychotherapy in the form of assurance. On the first visit I explain to them the nature of the condition, the diagnostic measures which may become necessary, the chronicity and the chances of recurrences. At the same time they are assured that we are dealing with a relatively harmless disorder and that in this era of antibiotics acute attacks and recurrences can always be brought under control.

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ENVIRONMENTAL ALLERGENS AS CAUSES OF ATOPIC DERMATITIS, AND THEIR MANAGEMENT

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Atopic dermatitis, or allergic eczema, can be and often is a troublesome affliction of children, especially in infancy and early childhood. It long has been considered strictly a local dermatologic problem and was treated like other "eczemas." In the absence of more definite etiologies, neurogenic or psychogenic factors were often considered of primary importance. Beginning in 1932, chiefly through the efforts first of Sulzberger and Coca[8] and later of Hill,[4] the allergic etiology was clearly established and the condition designated as *atopic dermatitis.*

ETIOLOGIC CONSIDERATIONS

Since these reports other demonstrations of the allergic nature of this condition were offered, especially as it affects children. Thus Hill and Sulzberger in 1935 were able to delineate three stages of the disease: the first affecting infants up to one or two years, the second affecting older children between two years and puberty, and the third affecting adults. Subsequently Hill and others were able to establish the etiologic importance of *food allergy*, especially in infants and young children, as determined by skin tests or clinical trial, or both. They found that removal of allergenic foods, especially egg, from the diets of these children was followed by improvement in the dermatitis, whereas reintroduction caused exacerbation.

But despite this apparently convincing evidence of the importance of food allergy, further clinical experience demonstrated that elimination

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of skin-test positive food allergens did not produce the expected beneficial results, especially in older children and adults and even in some younger children. Furthermore, wide discrepancy was noted between the positive skin reactions and the results of food withdrawal. As a consequence, many lost faith in these methods, and again became skeptical both about the relationship of food allergy to atopic dermatitis and about the value of skin tests in the diagnosis of atopic dermatitis.

One of the chief reasons for this confusion was the assumption that food allergens were the most important causative agents; hence, when the elimination of positive food reactors failed to relieve patients, the attending physician was led to believe not only that food allergy was not a factor, but also that skin testing was of no value in diagnosis. For some unknown reason *little or no attention has been given to the importance of inhalant allergens,* despite the fact that a possible relationship previously had been suggested by many writers,[1, 3, 6, 9, 14] even though none of the latter was entirely clear as to the manner in which the dermatitis was brought about.

In order to emphasize the significance of this relationship, in 1949, in the first of a series of studies, Tuft[10] reported the results of a study of 54 patients with atopic dermatitis in which, upon the basis of clinical and skin test evidence, house dust, pollens (especially ragweed) and wool were shown to be outstanding inhalant offenders; also that inhalants such as atmospheric mold, animal danders, silk, cooking odors, and so on, likewise were important offenders. In many patients included in that series clinical correlation could be obtained between the specific inhalant giving a positive skin reaction and the patient's eruptions.

Although the results of these studies confirmed the opinion of others that inhalant allergens were important factors in atopic dermatitis, the evidence upon which it was based still was purely clinical and hence subject to questionable interpretation. The author and his associates were able to obtain more convincing proof, however, in subsequent experimental clinical studies reported between 1950 and 1952. In the first of these studies[12] lesions of atopic dermatitis were induced repeatedly in susceptible subjects both by inhalation of the specific offending autogenous house dust in a powdered micronized form, and by injections of the specific house dust extract. Induction of similar lesions also followed inhalation of powdered Alternaria and injection of its extract. In addition, evidence was presented showing that the reaction apparently is mediated through the sweating mechanism.[13] Finally, in 1952, in a similar experimental and clinical study,[11] the eruption was induced in susceptible subjects both by inhalation of ragweed pollen and by injection of its extract, thus proving convincingly that seasonal inhalant allergens, notably ragweed pollen, could be and frequently were important etiologic factors in atopic dermatitis and deserved proper consideration in the management of this condition.

Actually, one need not be surprised that inhalants are important in atopic dermatitis, especially in older children. As already indicated, atopic dermatitis closely resembles allergic bronchial asthma; in fact, the two conditions have so many characteristics in common in relation to etiology, diagnosis and treatment that atopic dermatitis might properly be designated "asthma of the skin." Thus both conditions frequently coexist or alternate in the same patient. As in asthma, patients with atopic dermatitis are often worse in the winter, and especially at

the times of seasonal change. Positive skin reactions are obtained in about the same proportion in both conditions and have about the same clinical significance. Food allergens admittedly are more important than inhalants in asthma of infants and young children; on the other hand, inhalant allergens are more significant than foods in asthma affecting older children or adults; yet strangely enough, the same reasoning has not been applied similarly to the counterpart of asthma in the skin, namely, atopic dermatitis.

Because foods formerly were considered the major allergenic factors in infants and young children, little attention was given to the significance of inhalant allergens.

Tuft in a report published in 1955 therefore reviewed the case records of 76 infants and young children with atopic dermatitis to determine whether inhalant allergens are equally important. Since then an additional 9 children have been seen, making a total of 85 children. Review of this group of private patients shows that the age when the patient was first seen varied from infancy up to 12 years. Three were first seen in infancy, and 21 were 2 years old or younger and had the type designated by Hill as the infantile type; the remaining 64 had the childhood type.

Despite the varying age at which these patients were seen, the onset of the dermatitis in all but seven children occurred during the first year, usually in the first few months of life. Although some children were seen primarily because of the dermatitis, most of them came originally for a concomitant atopic condition, usually hay fever or asthma, or had the dermatitis subsequently.

All our patients had complete allergy studies, including history, physical examination and intracutaneous skin test. This was true even in infants or young children with extensive eruptions. In the latter patients, tests were done in the usually uninvolved skin areas of the upper and outer parts of the arms. If the eruption was so extensive as to involve the latter areas, testing was postponed until the skin in that area had sufficiently cleared. We recognized that under such circumstances indirect testing by means of the passive transfer technique advocated by Walzer could be done. But the performance of the latter method is not always easy or practical. We seldom had to use it in our patients, probably because nearly all, even those with generalized eruptions, had some skin area available for testing.

It has been said that tests done in the skin of patients with extensive dermatitis are neither accurate nor reliable. This was not true in our experience. The positive skin test reactions obtained in these patients were just as specific as in those with only flexural lesions. Thus we found that after the eruption had cleared up considerably and the skin generally was softer, retests with the extracts of the same allergens gave almost identical results. Of interest in relation to skin testing in patients with extensive atopic dermatitis was the observation that, even though the intracutaneous tests were done in an uninvolved area, a positive skin test reaction had a less clearly defined wheal and less intensive and demarcated zone of erythema than a positive test in the skin of patients either without dermatitis or in patients whose dermatitis was flexural in distribution and minimal in intensity. Furthermore, in doing the intracutaneous tests, it was observed that more pressure was required to insert the needle into the skin of patients with severe dermatitis, whereas when the skin was normal or nearly so, the needle penetrated the skin with ease. In fact, one could almost gauge the improvement in the skin condition by the ease with which the needle could be inserted. Upon the basis of the experience in skin testing both children and adults, I am firmly convinced that skin tests, whether by the scratch or intracutaneous method, are essential and should be a routine procedure in all children with atopic dermatitis.

Intracutaneous tests can be performed in the usually uninvolved skin of the upper outer part of the arm, whereas for scratch tests the back is

preferable. Testing should be done not only with extracts of those foods eaten by the patients, but also with the same common inhalant allergens (both seasonal and nonseasonal) as would be used in routine testing of a child with asthma of unknown etiology. Thus the inhalants tested should include house dust, animal danders, wool, pollens, molds, and so forth. All positive reactions should be retested at least once to make certain of their specificity; likewise, whenever possible, an attempt should be made to determine their clinical significance either by correlation with the original history or by clinical trial. This is easier to accomplish with food allergens than with inhalants; nevertheless it is sometimes possible after completion of the tests to obtain verification in retrospect of clinical sensitivity to such inhalants as house dust, animal danders, or wool. Often in my experience, when the tests are completed and the mother is told of the results, she will then recall instances in which certain positive-reacting allergens, whether inhalant or food, could have been responsible for an outbreak of the eruption or for its aggravation. This is indicated in Table 10, containing a summary of the allergy studies pertaining to inhalant allergens in our series. It will be observed that a clinical history of sensitivity especially relating to dust and wool was obtained in many of the children after the tests had been completed.

Knowledge of the specific allergens to which the child is sensitive

TABLE 10. *Results of Allergic Studies in Children with Atopic Dermatitis*

ALLERGEN	NUMBER OF CASES STUDIED	NUMBER AND DEGREE OF REACTIONS TO SKIN TESTS (I.C.)				NUMBER OF CLINICAL SENSITIVITIES	
		Neg.	Slt.	Mod.	Mkd.	By History	After Tests
House dust	84	1	15	50	18	0	**7**
Pollens:							
Ragweed	85	16	29	25	15	8	1
Timothy	84	56	23	2	3	1	0
Plantain	84	58	22	4	0	0	0
Molds:							
Alternaria	71	53	8	7	3	0	0
Animal danders:							
Feathers	84	30	41	13	0	0	0
Cat	83	71	11	1	0	1	1
Dog	83	73	10	0	0	0	1
Horse	83	71	7	4	1	0	2
Rabbit	81	76	5	0	0	0	0
Wool	84	33	49	1	1	6	24
Silk	78	62	12	4	0	0	**0**

according to the skin test results also makes the mother more aware of possible reasons for new outbreaks or for aggravation of old ones so that she is constantly on the lookout for explanations of new attacks. Such mothers no longer come in asking, "Why does Johnny have an outbreak?" but, instead, come in with the statement that "Johnny has a new eruption or is itching now because he ate some food he wasn't supposed to [or was in contact with wool, or a cat, or a dog, or was rolling around on the floor in a tussle with other boys]," and the like. This education of the parent in the detection of possible allergenic contacts to explain her child's attacks is one of the important and unrecognized benefits of the allergy study of the eczematous (or asthmatic) patient.

Inspection of the table shows that, as in asthma, all the inhalant allergens are not equally significant as causative factors of atopic dermatitis. The most prominent inhalant offenders in children, as in adults, undoubtedly are *house dust, wool* and *seasonal inhalant allergens*. The latter group will vary according to the plant flora of the particular region in which the patient resides; thus, in our own area representing the northeastern United States, the most frequent offenders are ragweed pollen and Alternaria. Other inhalants such as animal danders, silk, orris root, insecticides, and so on, play a definitely lesser role. These will be considered in more detail in the order named, purely for convenience and not to indicate their relative incidence.

House Dust

As in asthma, many children with atopic dermatitis have a positive skin test reaction to house dust (see Table 10). But the etiologic significance of this reaction in relation to the dermatitis is difficult to ascertain in children because one has to depend mostly upon clinical evidence and especially upon the results of treatment. Even though all children are exposed to house dust while crawling around the living room or bedroom on dusty rugs, it is difficult to correlate such exposure with the outbreak or exacerbation of the dermatitis. The latter might not be evident until 12 or 24 hours later and might be missed entirely. The delay in onset was demonstrated in our reported experimental studies which showed that induction or aggravation of the dermatitis after either the inhalation of the dust particles by the susceptible patient or the injection of the specific autogenous dust extract did not take place for at least 12 and in some instances 24 or more hours.

In the absence of an adequate clinical history which suggests that house dust exposure is etiologically responsible, one must rely upon such evidence as the relief afforded either by removal of the patient to another environment or by specific house dust desensitization coupled

with measures designed to lessen dust exposure. Both these methods have been used successfully in children with atopic dermatitis to emphasize the etiologic importance of house dust, as illustrated in the following case report.

CASE I. A girl, age 12, had flexural atopic dermatitis, recurrent since infancy and only symptomatically relieved by local dermatologic treatment. Allergy study showed positive reactions to dust, wool, pollens and some foods. The patient always improved while at the seashore in the summer. This was attributed to the beneficial effect of the sun's rays. She was always worse in early fall and winter months. She was asked to go to the seashore in the spring and, when she returned, to go to the home of a relative in the same neighborhood rather than to her own home. The skin condition cleared at the seashore. It did not recur even in a neighboring home of a relative, but became worse within a day or two after returning to her own home. Institution of proper dust precautions and desensitization with extract of an autogenous dust and of pollens were followed by improvement which persisted for the 3 years this patient remained under observation. During that period clinical trial determined that none of the positive-reacting foods, with the possible exception of chocolate, were of etiologic significance.

Here, then, is an example, illustrative of others, of a patient with atopic dermatitis present throughout her childhood and apparently due to sensitivity to her own environmental dust. This patient improved remarkably after reduction in her sources of dust contact plus dust desensitization. The results obtained showed that her improvement during the summer was due to removal from contact with the most important cause of the patient's dermatitis, her own environmental house dust, rather than to the beneficial effects of the sun's rays.

The question arises as to whether the house dust excitant can act in these patients also by direct contact as well as by inhalation. Since the lesions often involve the flexures, which usually are covered, the dust allergen will have little opportunity to act directly unless large amounts of dust come into direct contact with the skin. This may occur in infants or very young children who are allowed to crawl around the floor on dusty rugs. The manner in which the dust allergen may act was demonstrated clearly in one of our adult patients with hay fever, asthma and atopic dermatitis. She observed that when she dusted around the house with a cloth and enough dust came into direct contact with her skin, it caused itching and local eruption in the flexural area. But if she inhaled the dust when the flexures were covered, it first would cause her to sneeze and wheeze, and then, if the reaction was sufficiently intense, an itching eruption would appear in the affected flexures 12 to 24 hours later. It is obvious from this evidence that, regardless of the manner of operation, house dust can be and often is an important excitant in atopic dermatitis, not only in adults, but also in children; and that in the latter, though it more often produces its effects through inhalation, it sometimes can result from direct contact as, for example, in the following instance.

CASE II. A boy, age 6, had atopic dermatitis in infancy which improved after the complete elimination of egg from the diet. At 18 months the patient suffered coryza

and asthma in increasing severity which improved somewhat by symptomatic treatment. At 5 he had a recurrence of the dermatitis involving the ears, neck, forehead and, to a greater extent, both buttocks. The family history was strongly positive for allergy. The patient showed positive skin test reactions to various inhalants and food allergens, but especially to house dust, ragweed and Alternaria. Elimination and avoidance of test-positive allergens plus hyposensitization with extracts of ragweed and Alternaria were followed by improvement in the respiratory symptoms, but had little effect upon the dermatitis. Hyposensitization with house dust extract then was begun, and shortly thereafter there was noticeable improvement in the dermatitis. This improvement persisted during the period of observation except for mild asthma during the ragweed season, which was followed by slight but temporary exacerbation of the dermatitis.

In trying to determine why the dermatitis seemed to localize in both buttocks, which are unusual sites of localization in atopic dermatitis, the parents volunteered the information that the boy always preferred to sit on the floors instead of on chairs when indoors and on the ground when outdoors; also that he would keep rubbing the apparently itchy buttocks almost continuously while sitting. He rubbed himself so much that his underwear constantly was black with dirt. When this kind of contact was avoided, noticeable improvement in the dermatitis followed.

There seems little doubt in this patient, at least clinically, that the sensitivity to house dust was an important etiologic factor in the dermatitis, possibly through direct local contact.

Plant Pollen

Although the importance of pollen allergens in the production of atopic dermatitis was suggested in earlier clinical reports,[1, 2, 6] little attention was paid to them as possible etiologic factors. In the author's first study of inhalant allergens, in 1949, an unusually high incidence of positive skin test reactions to pollens, particularly to ragweed, was noted. In explaining the positive reaction in these atopic dermatitis patients it was pointed out that the pollen allergy could account in some patients for seasonal outbreaks of the dermatitis. The latter would occur either alone or along with a concomitant seasonal hay fever. A specific clinical relationship between the dermatitis and the pollen sensitivity was shown experimentally in a few patients by the induction of the dermatitis, not only after inhalation of the ragweed pollen, but also after injection of ragweed pollen extract either intentionally or accidentally. Although most of these observations concerned ragweed pollen, they applied equally to other pollens, especially timothy grass and English plantain, both of which are clinically less important in the eastern area, not only in atopic dermatitis, but also in hay fever.

A similar study of the importance of pollen allergy in 85 children with atopic dermatitis seen up to the present time shows that a large proportion (81.2 per cent) of the children had positive skin test reactions to ragweed, 47.0 per cent in moderate to a greater degree. A lower incidence of positive reactions to timothy grass and to English plantain was found.

When a child with atopic dermatitis has a positive skin test to a pollen such as ragweed, it becomes necessary to decide whether this reaction is of etiologic importance in relation to the dermatitis or whether it is related to such associated allergies as asthma and hay fever. Some of the children in our group had their attacks of dermatitis throughout the year as the result of allergy to either foods or inhalant allergens; but they also had seasonal exacerbations during the ragweed season. In such patients the positive skin test reaction to ragweed was an indication of a sensitivity which also was responsible for the dermatitis.

But in other children with perennial atopic dermatitis and a positive skin test reaction to ragweed there was no history of seasonal aggravation of the dermatitis. Some of these children had concomitant seasonal hay fever and/or asthma to account for the positive reaction to ragweed, but others had neither seasonal aggravation of the dermatitis nor associated hay fever or asthma. Under the latter circumstances the positive skin test to ragweed must be regarded as not having any immediate clinical significance and as being a nonclinical positive. Such a reaction may be the first evidence of the future development of hay fever in that patient, the skin being the initial tissue to be sensitized. This supposition is strengthened, first, by the fact that a family history of allergy, especially hay fever, is often obtained in these patients and, second, as shown by subsequent clinical observation, that some patients later have ragweed hay fever. This is illustrated in the following case reports.

Case III. A girl, age 5, was first seen at age 2 with atopic dermatitis present since infancy. Her parents were told by their pediatrician that their child would grow out of it, and only local applications were prescribed. The family history was strongly positive for allergy. Positive skin reactions were obtained to house dust, wool, *ragweed*, milk and a few other foods. Her condition was greatly improved by eliminating milk and wool; also by minimizing house dust contact and by going to the seashore. When first seen, the patient had no hay fever symptoms, nor was there any flare-up during the ragweed season despite a positive skin reaction. But for the first time, while at the seashore in August, 1949, she had mild hay fever symptoms accompanied by a mild outbreak of atopic dermatitis.

Case IV. A 3-year-old girl was first seen in April, 1947, with flexural atopic dermatitis involving the antecubitals, wrists and popliteals and present constantly since the age of 18 months with no apparent seasonal aggravation. Intracutaneous skin tests were positive to such inhalants as house dust, feathers, orris root and wool, to several foods, and in slight degree to ragweed pollen despite the absence of clinical hay fever. After elimination of the test-positive foods and avoidance of the offending inhalants (notably wool) the eruption disappeared so that specific desensitization was considered unnecessary. In September, 1951, the patient had typical symptoms of ragweed hay fever associated with mild wheezing which responded to routine symptomatic treatment.

Therefore a positive skin test reaction to ragweed pollen obtained in children with atopic dermatitis sometimes has no etiologic relationship to the dermatitis, but may be due to an associated hay fever, either present at the time the patient is seen or appearing some time in the

future. Under those circumstances the dermatitis in these patients is not due to pollen sensitivity, but to other nonpollen factors. But in other patients the pollen allergy is definitely a factor in the dermatitis. Thus, for example, 17 of the children in our series had seasonal outbreaks of atopic dermatitis from ragweed pollen allergy. Thirteen of these also had an associated hay fever. The remaining four patients had perennial dermatitis from various nonpollen causes, but suffered seasonal aggravation of the dermatitis.

Evidence of the etiologic importance of the ragweed pollen was furnished in our previously reported study[11] by induction of the dermatitis both by inhalation of dry ragweed pollen and by injection of ragweed pollen extract into two volunteer subjects. But it sometimes can be induced accidentally as part of a constitutional reaction which may follow the injection of pollen extract for treatment. This is illustrated in the following case report.

CASE V. A girl, aged 6, was seen because of seasonal hay fever and perennial allergic rhinitis of 3 years' duration. She had "eczema" during infancy, but this disappeared during her second year of life. After completion of allergy studies preseasonal ragweed pollen therapy was begun. Shortly thereafter on 2 occasions the patient had an itching, papular eruption in the antecubital, thigh and chest regions after the injection of ragweed pollen extract in small dosage (0.0006 total nitrogen), necessitating reduction in dosage. The eruption finally disappeared, but recurred in mid-September in the antecubital, thigh and popliteal areas and persisted for about 2 months. At that time the mother recalled that about the same time during the previous hay fever season, before the child had received treatment, a similar eruption had occurred, but was attributed to "prickly heat." There was no further recurrence of the eruption during the subsequent 4 seasons pollen therapy was continued, and only mild hay fever symptoms were experienced.

This case illustrates the induction of dermatitis after ragweed injections; also seasonal outbreaks of atopic dermatitis in hay fever patients which may be missed unless one watches for it.

Appreciation of the possible role of pollen sensitivity in atopic dermatitis therefore is essential to proper management of these patients. If a causal relationship can be established by history or skin test findings, or both, pollen desensitization is definitely beneficial. In the absence of a definite history of seasonal aggravation, but with positive skin test reactions to pollen, it is difficult to decide whether pollen therapy is advisable. If a child with mild nasal symptoms has a positive family history of hay fever, pollen therapy may be helpful prophylactically even if the pollen sensitivity has no bearing on the skin condition; and from long personal experience with its use I am sure that it has been beneficial to many children.

Atmospheric Molds

Molds also are important inhalant excitants in atopic dermatitis, especially in those regions where mold allergy is prevalent; as, for example,

the midwestern or grain areas of the United States. In the eastern areas the incidence of mold allergy in hay fever or asthma patients is rather low (only about 5 per cent); and, by inference, this probably also is true of patients with atopic dermatitis. Thus of the 71 children tested with Alternaria, only 18 had positive reactions, 10 being in moderate to severe degree. Although some of these positive reactions undoubtedly were clinically significant, it was much harder to establish an etiologic relationship in these patients than in those positive to pollens. In our experimental studies, however, we were able to induce outbreaks of atopic dermatitis in one patient after inhalation of powdered Alternaria[13] and also by injection of its extract, proving a causal relationship. On the basis of these findings atmospheric molds must be considered important excitants of atopic dermatitis and should be included in the management of these patients, especially in patients in whom pollen hyposensitization is being utilized.

Animal Danders

These also may be important causes of atopic dermatitis, but, as in asthma, the exact incidence is difficult to estimate. Thus many children had slight or moderately positive skin test reactions to *feather extracts.* But it was not easy in those instances to decide whether such reactions were etiologically important, because a clinical relationship cannot be easily proved. Other danders, including *horse, rabbit, cat* and *dog,* are not prominent causes of atopic dermatitis, probably because of lessened opportunity for contact. From 10 to 15 per cent of the children studied gave positive skin reactions to extracts of these danders, but it was not always possible in these patients to verify the clinical significance of these positive reactions. Two children, however, had definite itching of the affected skin areas, or new outbreaks, after contact with a horse, one after contact with a dog, and another after being near a cat. Improvement in the skin condition was noted after avoidance of contact with the animals. As in asthma, positive skin tests with extracts of cat, dog, horse or rabbit epithelium often are clinically significant, so that when such reactions are obtained in patients with atopic dermatitis, one should search diligently for possible sources of contact to prevent aggravation of the dermatitis.

Wool

The importance of wool as an etiologic factor in atopic dermatitis is unquestioned. But whether wool acts as an inhalant or as a contactant, or whether it causes aggravation by nonspecific irritation is not always easy to determine. Thus 30 of the 84 children studied stated definitely

that they could not tolerate wool contact, that itching of the skin or actual eruption followed when wool was brought into contact with their skin lesions or even with the unaffected skin. Undoubtedly, in some of these patients a direct contactant and perhaps irritant effect is responsible, and perhaps the eruption in these instances is not due to specific sensitization. Nevertheless, many patients showed definite improvement when woolen clothing or bedding or rugs were removed completely. Since these are not always in direct contact with the patient's lesions, one may assume that some of the wool allergen entered the circulation after being inhaled. As with feathers, the incidence of positive skin tests with wool extract usually is high (60.8 per cent of the 84 children), but the tests are not always indicative of specific sensitization. Regardless of the mechanism, however, wool is an important allergenic factor. It therefore is essential that all patients with atopic dermatitis eliminate wool contacts.

Silk

A similar situation exists in relation to silk. Patients with atopic dermatitis may show positive skin reactions to this allergen. About one fourth of the children tested showed positive skin reactions, four in moderate degree. But none of these patients were aware beforehand that they were clinically sensitive, since this is not easy to detect. Evidence that silk can be responsible for aggravation of symptoms in patients with atopic dermatitis already has been furnished by others.[3, 9] But as with wool, although the allergic reaction probably results from direct contact of the silk with the patient's skin, Sulzberger and Vaughan[9] conclusively demonstrated that silk protein, after being inhaled, is absorbed into the circulation. It therefore can aggravate or induce the lesions of atopic dermatitis. It is not easy to determine in a silk-sensitive patient which route is operative. Patch tests usually are negative, but this fact does not exclude a possible contactant action. Regardless of the mode of action, all possible sources of silk contact should be removed from children who have positive skin test reactions to silk.

Other Allergens

Other inhalant allergens, including *orris root, tobacco, insecticides, goat hair, cereal flours,* and so on, are infrequent causes of atopic dermatitis in children. Thus occasional instances of atopic dermatitis in adults have followed the inhalation of cereal flours (e.g., in bakers), but this would be rare in children. Even the inhalation of perfume or of highly scented cosmetics, or of cooking odors[5] such as fish may aggravate the dermatitis in some patients.

Human Dander

Interest again has been revived in possible sensitivity to human dander as a cause of atopic dermatitis, especially in infancy. Allergy to human dander first was described in 1925 by Van Leeweun, who considered it important in bronchial asthma. But this was never clearly proved, and the subject was dropped. Simon[7] showed that infants with atopic dermatitis gave positive skin reactions and passive transfer tests to human dander. He believes that in such instances the human dander present in the scalp of the mother or father may aggravate the lesion, either by direct contact with the skin or possibly after inhalation. No definite etiologic relationship has been established in these patients. Until it is, one must withhold judgment as to whether human dander is a specific causative inhalant factor in atopic dermatitis, although it does no harm to eliminate this possible source of irritation.

CLINICAL MANAGEMENT

Recognition that inhalant allergens can be important causative agents in atopic dermatitis affecting children is essential to its proper clinical management. Failure to utilize this newer knowledge may be responsible for frequent failures in treatment, especially in older children. When a child with atopic dermatitis is first seen, his attending physician usually assumes that if the condition is allergic, food allergens are the most likely excitants. Attempts are made to determine this either by skin test methods or by diet trial, or by a combination of both procedures. These efforts often are rewarded, especially in infants or young children, by detection of the offending foods; their subsequent elimination sometimes is followed by remarkable improvement in the dermatitis or its complete disappearance; as, for example, in the following illustrative case reports.

Case VI. A girl, age 3 years, had generalized atopic dermatitis involving the cheeks, neck, popliteals and antecubital spaces since the age of 18 months, unrelieved by various local medicaments. Her sister had hay fever, and her maternal grandmother had hives. Intracutaneous skin tests showed positive reactions to egg and wheat and to certain clinically unimportant foods. After elimination of wheat and egg there was progressive improvement in the skin condition, with complete clearing in less than 2 months. Five years later the mother, after a follow-up inquiry, reported that the child's skin remained clear so long as she adhered to her diet, whereas ingestion of egg and wheat would be followed by an eruption.

Case VII. A girl, age 2, had severe atopic dermatitis involving the entire face, which showed numerous bleeding excoriated areas and secondary crusting. There was similar but less severe involvement of the antecubital and popliteal spaces. The dermatitis began at the age of 3 months and was recurrent, being less intense in the summer and worse after late September. The mother was told by the attending dermatologist that the child would grow out of it. The mother had hay fever, and a maternal cousin and maternal great-aunt had asthma. Positive reactions were obtained to ragweed, dust, feathers, wool and the following foods: wheat, pork, chocolate, green pea,

spinach, tomato and orange. The patient showed progressive improvement during the testing period, particularly after elimination of both the test-positive foods and of egg. The latter was eliminated from the diet when the patient was first seen and was not added back even though the skin test to it subsequently was negative. By the time the tests were completed there was almost complete clearing of the eruption. When she was seen again 6 months later, the skin condition, especially of the face, was excellent and there remained only slight involvement of the ear lobes. She had remained well in the interim except on one occasion when she had a slight eruption of the face following a "head cold" which disappeared in a short time.

CASE VIII. A boy, age 22 months, had atopic dermatitis of the antecubitals and popliteal spaces since early infancy. His mother and brother had hay fever. Intracutaneous skin tests showed positive reactions to dust, wool, ragweed, Alternaria and the following foods: milk, wheat, chocolate, green pea and tomato. Some improvement was noted after inhalant avoidance and elimination of milk, but complete clearing did not occur until after elimination of the other test-positive foods, especially tomato and chocolate. The patient had recurrences on several occasions during the subsequent 4-year period of observation, but these always could be traced to dietary indiscretions.

These reports illustrate the etiologic significance of food allergy and the remarkable improvement in the dermatitis which followed removal of the test-positive foods. In case VI the two most important causes of the child's dermatitis, namely, egg and wheat, were detected by skin testing, a procedure which had been opposed by the attending pediatrician. He thought the child too young to be tested and also that skin tests were valueless in atopic dermatitis. The fallacy of such thinking, which unfortunately is shared by others, has been disproved conclusively by our own experience, as exemplified in the illustrative case reports included in this presentation.

In case VII egg was eliminated completely from the child's diet from the outset, even though skin tests to egg later proved negative. This was done because of the observation by Hill that egg is the most common food allergen responsible for atopic dermatitis in young children. Just why the skin test to egg is negative in clinically positive patients is not known.

One cannot emphasize too strongly the necessity for skin testing, not only with food allergens, but also with the important inhalants. Although infants are more likely to show allergy to foods and older children to inhalants, these patients, like the asthmatic, can be sensitive to more than one allergen; thus they may be allergic to more than one food or more than one inhalant, or both to inhalants and to foods, or to seasonal and nonseasonal inhalants, such as ragweed and house dust. Therefore, if positive tests are obtained to dust and/or to wool as well as foods, the mother should be instructed as to the manner in which contacts with these allergens should be avoided. This may aid both in the treatment of the existing dermatitis and as a preventive measure against future sensitizations. Likewise in older children in whom inhalant allergens often are more important than foods, one must remember that unrecognized food allergy may cause aggravation of the dermatitis and impede a satisfactory outcome as, for example, in case VIII.

In some patients, especially infants, the dermatitis may be due to allergy to one or two allergens (as, for example, egg and wheat in case VI). Removal of these foods from the diet may result in dramatic improvement in the dermatitis resembling the quick relief sometimes seen in asthmatic children after removal of an offending cat or dog from the house. But in most children, particularly the older ones, the dermatitis is caused by more than one allergen, and unless all possible excitants, both inhalant and foods, are treated or eliminated, good results cannot be expected. This is illustrated in the following cases.

CASE IX. A boy, age 7, had atopic dermatitis of the antecubitals, popliteals, groin and trunk, recurrent since infancy. The only positive family history was "eczema" in a paternal uncle. Positive intracutaneous skin tests were obtained to house dust, feathers, wool, ragweed (slight) and to several foods: wheat, chocolate, pork, spinach and tomato. Improvement followed hospitalization, with immediate recurrence upon return home, despite attempts at inhalant avoidance and exclusion of test-positive foods from the diet. Hyposensitization with an autogenous dust extract was begun, and within a month or two definite improvement was noted. The skin remained fairly clear thereafter, but erupted mildly whenever the patient deviated from his diet. Wheat, chocolate and tomato were the most frequent offenders. The patient was followed up for more than 3 years, at which time all treatment was discontinued. At that time his skin was clear, and he was able to tolerate a fairly general diet without skin eruption.

CASE X. A girl, age 4, had atopic dermatitis of the face, antecubitals, wrists, and back of the neck present since the age of 11 months, worse in late summer and after wool contact. A maternal cousin had eczema, and another had asthma. Positive intracutaneous skin tests were obtained to house dust, wool, ragweed, chocolate, corn, spinach, tomato and orange. Some improvement was noted after avoidance of the test-positive allergens, notably wool; but complete relief was not obtained until hyposensitization with extracts of autogenous house dust and ragweed had been given. Mild recurrences affecting the antecubital fossae followed on different occasions after ingestion of chocolate or contact with feathers, dog hair or dust. After 2 years of treatment the skin was entirely clear, and the patient was discharged.

Cases IX and X illustrate the value of complete allergy studies in the management of these patients. Unless every possible etiologic factor is determined, the skin condition will either remain stationary or worsen. Corroboration by clinical evidence is always desirable, but is not always obtainable. For example, if a patient improves after hospitalization (as in case IX) or change of residence (as in case I), this fact suggests sensitivity to house dust. Likewise, the beneficial effect of hyposensitization treatment with extracts of offending inhalant allergens such as pollens, molds or dust also attests to the clinical significance of those allergens. More definite proof of a causal relationship may be furnished by induction of the dermatitis after inhalation of the suspected inhalant; but this is not often possible or practical, especially in patients with concomitant respiratory allergies.

The treatment of children with atopic dermatitis can be greatly simplified if the patient is treated as though he has allergic asthma instead of dermatitis. All patients, even infants, should be tested with the foods they are eating and with the important inhalant allergens. If positive

skin test reactions are obtained, efforts should be made to establish their clinical importance either by more thorough history or by clinical trial. Test-positive foods should be eliminated from the diet, and avoidance of contact with the offending inhalant allergens carried out. If the patient improves, no further treatment is necessary, as happened in cases VI, VII and VIII. After the skin has cleared up completely the test-positive foods may be added back one at a time to determine which ones must be avoided.

Elimination or avoidance may be easy with food allergens or with inhalants such as feathers or animal danders. It is difficult with such inhalants as house dust, pollens and/or molds. If wool is a factor, substitutes should be provided (e.g., a cotton quilt for a woolen blanket, or cotton, rayon or Orlon sweaters instead of wool), or the wool should be covered in such a manner as to prevent its coming into direct contact with the skin or from being inhaled (as by lining woolen snowsuits for children with cotton materials). When inhalant contact cannot be completely avoided, specific hyposensitization may be required. This is true especially with house dust, pollens and molds. Hyposensitization with extracts of animal danders or with wool is not too effective and seldom is required.

Hyposensitization with the extracts of inhalant allergens, such as house dust, ragweed and/or timothy pollens, and atmospheric molds such as Alternaria and Hormodendrum should be carried out in the same manner as in patients with asthma and/or hay fever. But certain precautions should be taken to prevent the development of reactions. The problems entailed in hyposensitization treatment in these patients have been reviewed by the author in a separate report (now in press). Thus, of 125 patients (both adults and children) with atopic dermatitis who received hyposensitizing injections of extracts of inhalant allergens, 34 patients had a total of 49 reactions. The reaction usually was temporary and could be obviated by reducing the dose and later increasing it more gradually. But in five patients, all with generalized eruptions, reactions consistently followed extremely minute dosage, and subsequent attempted increases in dosage resulted in aggravation of the dermatitis rather than its amelioration. The reactions which followed the injections usually were delayed in onset for 12 to 24 hours or longer and therefore may go unrecognized, unless one is aware of this delay. Reactions are characterized either by aggravation of an already existing dermatitis or by the appearance of new lesions, as happened in case V and as is illustrated in the following case report.

CASE XI. A boy, age 4½, had atopic dermatitis of the cheeks and buttocks present since early infancy. His mother had had eczema in childhood, his father has hay fever, and his paternal grandmother had asthma. Skin tests were positive to dust, feathers, wool, ragweed and the following foods: chocolate, green pea, spinach, tomato and cinnamon. Improvement was noted after elimination of test-positive foods, with re-

currence after addition of chocolate and cinnamon; but clearing did not follow until autogenous dust hyposensitization had been given. On several occasions injection of 0.5 cc. of a 1:100 concentration of autogenous house dust was followed by recurrence of the eruption on the cheeks. The dose was reduced and built up gradually to a maximum tolerated dose of 0.3 cc. of a 1:5 dilution.

Reactions from treatment in the dermatitis patient are much more discomforting, last longer, and are not as easy to control as are reactions in the asthmatic, who can be relieved quickly by an injection of epinephrine. But in the patient with an induced dermatitis the eruption may not clear for several days or longer. The dosage must be administered with sufficient care to avoid reactions. The extracts used should be diluted much more than those used for the asthmatic—even by 100-fold or 1000-fold until one is certain no reaction is provoked. If the patient can tolerate this dosage, then the dose is increased slowly until the maximum tolerated dose is reached. Despite these precautions we have induced aggravations of the dermatitis in some patients, particularly those with generalized eruptions, after the injection of almost infinitesimal doses of extracts. For example, one patient repeatedly got reactions from 0.1 ml. of a 1:100,000 dilution of dust extract, and another from 0.1 ml. of a 1:1,000,000 dilution. Whenever such reactions occurred, the dosage was decreased and kept stationary until no further reactions were noted.

To minimize the possibility of reaction, in the past 4 years I have administered the diluted extracts intracutaneously, beginning with a highly dilute solution (1:1,000,000 or 1:100,000) in doses of 0.01 ml. and increasing 0.01 or 0.02 ml. until 0.1 ml. was being given. Then, if no reaction occurred, the next higher concentration was given. Since this method has been adopted, fewer reactions have been noted.

If these precautions are observed, good results will be obtained, but only in those patients who persevere in the treatment despite temporary aggravations or setbacks brought on by unexpected inhalant contacts or at times by the hyposensitizing injections. As in hay fever, no one can predict just how long the patient must be treated before improvement or complete relief occurs. In some patients six months to two years has been sufficient, whereas in others a much longer period is required. All that one can say is that with proper allergy treatment in the manner just outlined, most patients will improve, whereas, if allowed to go untreated, the dermatitis can become more widespread with increased chronic thickening of the skin (ichthyosis) and possible superimposed secondary infection.

SUMMARY

Inhalant allergens, especially house dust, plant pollens, atmospheric molds, and wool, are additional important excitants of atopic dermatitis

in children. Failure to appreciate this has been responsible for past failures in treatment, whereas their detection and correction often are followed by noticeable and lasting improvement. All children, no matter how young, who have atopic dermatitis should be investigated routinely for both food and inhalant allergy. Treatment in these patients, as in the asthmatic, should consist in elimination or avoidance of test-positive allergens (both food and inhalant) and hyposensitization when necessary. Greater care in dosage regulation will prevent aggravation of the dermatitis, since reactions are delayed in onset and easily overlooked. If proper precautions are observed, good results will be obtained in most patients, provided they are willing to cooperate and to persevere with treatment.

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URTICARIA

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THE CLINICAL PROBLEM

Let the reader ask himself some frank and searching questions, mostly in the first person singular, about his experience with urticaria.

How many times have I resolved a case of urticaria by discovering *the indubitable cause*, and then cured it right away by removal of that cause or by permanent interference with it in some other satisfactory manner? When did that last happen? Has it ever happened to me?

How many (more) times have I failed to resolve cases of urticaria as to their causes and then failed to cure them by any means? How many times did I stab at causal possibilities, thought I had the cause in a particular case, and then have it, and any sort of cure, exasperatingly elude me?

In those cases of urticaria in which I proved the cause—*beyond a doubt*—how did I do it? Did I do it by sharp history-taking and then by the tests of avoidance (which cleared the condition) and by at least one test of re-exposure (which caused it to recur)? Or did I do it purely by scratch and intradermal testing with a large number of unselected, common food and inhalant allergens? Or did it take a combination of ingenious analysis of history and painstaking laboratory and clinical tests? Did I discover single or multiple causes?

When I discovered unequivocal causes, what were they? How often foods? What foods were they? Nuts, for example? What nuts? Fish? What fish? Berries? Which? Strawberries? Cereals? Which ones? Meats? What meats? How often drugs? What drugs? How often inhalants? Which? How often focal microbial infections or helminthic infestation? Of what organs and what organisms? How often psychopathic states? Of what nature?

Cause discovered, how did I achieve cure? By being able to enforce strict avoidance of the cause? By hyposensitization with graded administration of the offending agents? By use of counteracting drugs (antihistaminics, adrenocorticosteroids, epinephrine, ephedrine, calcium gluconate)? By extirpation or sterilization of foci of infection? By psychiatry? By prayer?

When cure was not achieved either because cause was not discovered or because, even discovered, cause was not avoidable or removable, or not susceptible to counteraction by drugs or hyposensitization techniques or psychiatry, what was the fate of the patient and the condition? Did the patient just disappear from observation, to my great relief? Did the condition cease at long last, also to my great relief, though the reasons for this were as mysterious as its cause? Or did the condition go on interminably both to the patient's and my great distress?

What are the honest and true answers to these questions? Are they not that indubitable causes of urticaria are rarely discovered, that reasonably expeditious cures are rarely achieved, and that no one is really comfortable or confident about managing such cases?

Finally, can this over-all sorry situation as to discovery of cause and achievement of cure of urticaria be bettered?

Let us try.

THE MECHANISM OF WHEALING

It is necessary first to review some basic science aspects of the whealing mechanism. The primary lesion of urticaria is the wheal (or hive), i.e., a solid elevation of the skin that develops suddenly and quickly (within seconds to minutes) and disappears relatively rapidly (within hours), eventually leaving no trace. The wheal is acute, circumscribed edema and, like all edema, is predicated upon blood vessel dilatation, increased end-vessel permeability and exudation of fluid (plasma) into surrounding tissue. It is an aspect or a species of inflammation. In the case of the wheal of urticaria, unlike other forms of inflammation, the dilatation of blood vessels and the increased permeability of their walls are brief and shortly reversed; the exudation of fluid is prompt and sharply defined; and finally, resorption of exuded fluid is rapid (relative to other forms of edema) and complete.

In the normal course of things, blood vessel caliber and vessel wall permeability vary constantly though slightly, and fluid exchange between blood vessel and intercellular circulation goes on properly and unceasingly within asymptomatic limits. Physiologically, we shrink and swell a little and irregularly. Pathologic alteration of body fluid partition (in the direction of swelling, more than of shrinking) begins at the point of signs, symptoms and disturbances of average function.

There are many agents and agencies that cause instantaneous, excessive blood vessel dilatation and increased blood vessel permeability to degrees that permit passage of abnormal amounts of plasma fluid outward into tissue. Histamine is one such agent. Physical injury by mechanical force (friction, pressure), heat, cold, and ultraviolet light, certain antigen-antibody interactions (allergic reactions) and certain drugs and venoms are well known promoting agencies. Histamine is a naturally occurring metabolite (a degradation product of the amino acid histidine) which is produced in certain physiologic amounts in average metabolism and in greater amounts under the influences of agencies such as those just listed. The mast cell seems to be a unit that has much to do with the elaboration or storage of histamine and regulation of its release into the general vascular or local tissue circulation. When histamine is produced or released in normal amounts, the normal range

of things happens, but when produced or released in excess, as in certain amounts of trauma to tissue, in certain extreme intensities and durations of heat, cold, and electromagnetic energy and in certain antigen-antibody interactions, then pathologic degrees of swelling (urticarial edema) always occur. Certain drugs, e.g., morphine and related alkaloids, and venoms "liberate" excessive amounts of histamine; partially degraded proteins (polypeptides) endogenously produced or exogenously introduced may contain histamine in large, highly reactive amounts. Whatever else may biochemically induce edema (as urticaria or more profound inflammation), histamine is surely one such mediator, perhaps the one absolutely necessary for urticaria.

GENERAL DIAGNOSIS AND CLASSIFICATION OF THE URTICARIAS

Many dermatoses have wheals or wheal-like components as part of their clinical appearances, but the lesions of the conditions that are designated simply as urticaria or hives are monomorphous and uniform in their evolution and involution. There are several types of urticaria that are distinguishable by variations in form, size, location, symptomatology and duration of wheals, and sometimes by easily detectable mechanism, but always there is the common denominator of circumscribed swellings which develop rapidly, stay rather briefly and disappear without sequelae, and, depending on operation of continuing or recurring cause, repeat in the same manner. For example, the form and size of the wheal may be small and round (match-head to pea size) in so-called cholinergic urticaria and papular urticaria of insect bites, moderate in size (coin to large nut size) and round or irregular with a tendency to enlarge by coalescence in banal acute and chronic urticaria, large and irregular (fruit to palm size) in angioneurotic edema, and linear or bizarre-shaped and variable in size in "physical" urticaria (depending on the geometric design of the physical mechanism). The location of the wheals may be anywhere and fickle in banal acute and chronic urticaria or repetitively fixed about the eyes, mouth and hands or feet in angioneurotic edema, on exposed portions of the body in the "papular" urticaria of insect bites, or at points of friction and pressure of garments and at the accidental sites of friction and pressure of ordinary events in urticarial dermographism. In symptomatology most wheals itch, but within a large variability of very little in some forms to maddening intensity in others. Finally, at the extremes, there are cases of urticaria that amount to no more than a mere blush, and others that eventuate into vesicles or bullae (strophulus) or hemorrhage (purpura).

We are now at a point at which we may attempt classification and etiologic discussion of the urticarias. In considering the complexity of the biochemical basis of urticaria (at least that of histamine action)

and the multiplicity of mechanisms or agencies that may set that biochemistry in motion, no simple classification is satisfactory. Descriptive rather than nominal classification is necessary for deep understanding. For didactic purposes I would suggest a classification that rests at least upon factors of spontaneous total duration and something of causal possibilities. Thus:

1. Acute urticaria and angioneurotic edema resulting from allergic sensitization to ordinarily harmless substances or from primary urticariogenic agents which, in both cases, act but briefly, and/or to which exposure, in both cases, is only occasional
2. Chronic or recurrent urticaria and angioneurotic edema resulting from allergic sensitization to ordinarily harmless substances or from primary urticariogenic agents which, in both cases, act for long periods, and/or to which exposure, in both cases, is frequent
3. Special types of urticarias
   A. "Physical" urticaria resulting from agencies such as mechanical trauma (stroke, friction, pressure), heat, cold, and electromagnetic energy (limited ultraviolet light ranges)
   B. "Papular" urticaria resulting from venoms injected by stings and bites of insects and metazoa of other orders or from sensitization to other of their products that are ordinarily harmless
   C. "Cholinergic" urticaria

ACUTE URTICARIA AND ANGIONEUROTIC EDEMA RESULTING FROM ALLERGIC SENSITIZATION TO ORDINARILY HARMLESS SUBSTANCES OR FROM PRIMARY URTICARIOGENIC AGENTS WHICH, IN BOTH CASES, ACT BUT BRIEFLY AND/OR TO WHICH, IN BOTH CASES, EXPOSURE IS ONLY OCCASIONAL

This predication describes an explosive episode of wheals and attendant pruritus that lasts for a day or two to a week or two and then ends. The condition may be as mild as a few hives that come and go in the customary manner, itch moderately and cease in the short prescribed time, or it may be so severe that the entire skin surface is at times one vast hive, discomfort is extreme, and life may be endangered by the vastness of the process, which may involve other organs such as lungs, heart and brain.

The cause of some such fairly common experiences can occasionally be quickly traced to a particular substance (horse serum, penicillin) and a particular circumstance (injection of such substances for an illness or in anticipation of an illness). More often such obvious things as serum sickness or allergization and allergic reaction to a common drug occurring under one's personal observation are not found, but since the usual case of acute urticaria ends fairly quickly and ordinarily does not recur with a frequency that compels seeking of more attention than the short-enduring attack demands, it would seem to become an academic exercise to speculate on, or to prove, the specific cause of a particular case that is over before long. It is always valuable, however, to speculate on, and investigate for, possible pathogenic mechanisms, even

in the mildest of cases, purely to know and possibly to gain understanding of causes in those cases of acute urticaria that may be the beginning or first episode of a long course of chronic, recurrent urticaria.

Study of the immediately antecedent and concurrent history of many cases of acute urticaria that are going to be of short duration frequently reveals events such as an illness, particularly gastroenteritis associated with overindulgence in alcohol and sumptuous meals, or the taking of common anodyne or sedative medicaments. Such situations occur in strenuous ceremonial activities such as marriage parties, anniversaries, celebrations of good fortune and exercise of plain high spirits. In the world of the child, comparable events are picnics and birthday parties, and the gastronomy runs to frankfurters, soda pop, cake and ice cream. As everyone who leads a full life to its full foolishness will remember, such circumstances frequently result in fatigue, malaise, dyspepsia, grippiness or some other vague form of systemic indisposition.

In this condition two likely causes of urticaria may operate: namely, (1) the taking of medicines such as salicylates and coal tar derivatives (acetylsalicylic acid alone or proprietaries containing acetylsalicylic acid, acetanilid, phenacetin, caffeine and quinine), opiates (codeine, paregoric), and atropine or atropine-like agents (belladonna, synthetic sympatholytic agents) for the hangover or other indisposition; and (2) the absorption by an inflamed gut of polypeptides, i.e., partially split proteins and other incompletely digested products.

Of the drug possibilities, the opiates and atropine alkaloids are primarily urticariogenic; that is to say, they cause hives from an inherent pharmacologic action (histamine "liberation") and may, even in average doses, under the circumstances of illness, conceivably cause explosive, short-enduring episodes of urticaria. In a similar manner, incompletely split proteins are notably urticariogenic (by histamine content?). No allergic mechanism is involved in the latter instances, but rather that which would happen to anyone who received a subcutaneous or intravenous injection of the alkaloids or polypeptides in point. When an allergic mechanism involving a drug or a protein complex is at play, it is because of prior or concurrent sensitization to that drug or that protein complex absorbed in the adventitious manner described above. In the case of a drug cause, whether by sensitization or primary urticariogenic mechanisms, an episode of urticaria would be acute and of short duration if the drug exhibition is a solitary administration, and that of a drug that does not linger in the body for a long time; repetitive taking of such a drug would convert the case into one of chronic, recurrent urticaria.

If true protein sensitization on an allergic basis, or primary urticariogenic polypeptide absorption, should be the operative mechanism, the clinical event ought to persist only as long as gastrointestinal inflamma-

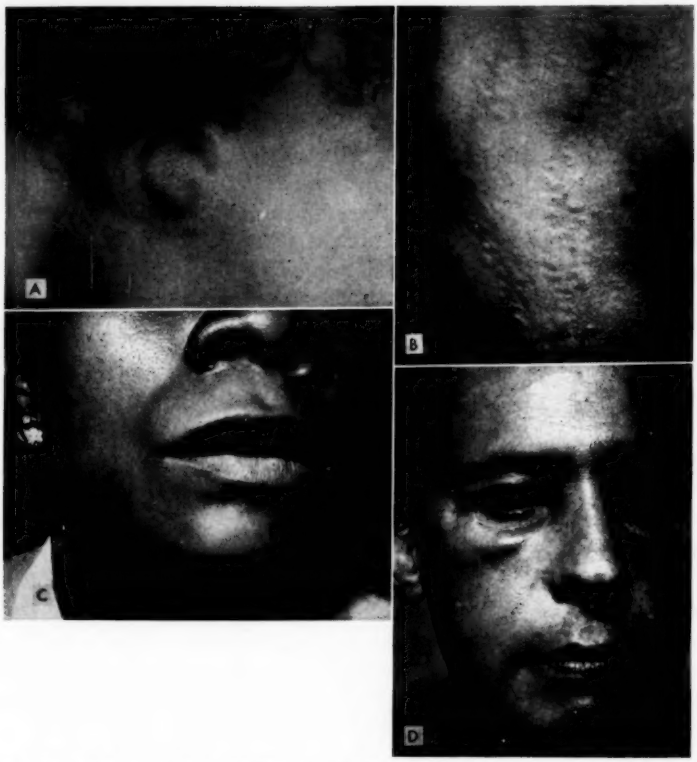

Fig. 20. *A*, Common form of discrete whealing frequently seen in acute and chronic urticaria. *B*, Common form of confluent whealing frequently seen in acute and chronic urticaria. *C*, Angioneurotic edema involving the upper lip. *D*, Angioneurotic edema involving the region of the eyes. (From the Collection of the Skin and Cancer Unit of the University Hospital of the New York University-Bellevue Medical Center.)

tion permits absorption of that particular peptide complex, and ought to cease upon gastrointestinal restoration or upon metabolic or other elimination of what was absorbed improperly.

Of the two likely pathogenetic mechanisms and classes of causative substances, the operation of primary urticariogenic agents rather than allergic reaction to ordinarily nonurticariogenic materials is probably more common in acute urticaria. Those cases of acute urticaria that are rooted in allergic sensitization to a common substance tend to develop into the chronic, recurrent variety unless discovery, elimination and avoidance of that substance are expeditious and complete for all time.

Whatever may be the true conditions in acute, short-lived urticaria, the situation is happier than in other urticarias because it is relatively quickly over or quickly suppressible by modern therapy.

CHRONIC OR RECURRENT URTICARIA AND ANGIONEUROTIC EDEMA RESULTING FROM ALLERGIC SENSITIZATION TO ORDINARILY HARMLESS SUBSTANCES OR FROM PRIMARY URTICARIOGENIC AGENTS WHICH, IN BOTH CASES, ACT FOR LONG PERIODS AND/OR TO WHICH, IN BOTH CASES, EXPOSURE IS FREQUENT

Chronic, recurrent urticaria caused by allergic sensitization to ordinarily nonurticariogenic substances is a more common and more formidable problem than any other type of urticaria. The clinical picture is familiar in the form of frequent (hourly, daily or more widely spaced) unpredictable episodes of eruptive wheals of variable sizes (nut-, egg-, palm-sized), of variable shapes (round, plaquelike, confluent and gyrate) and in variable sites (localized or generalized). A story of such trouble for more than two or three weeks means trouble for an uncertain long time unless resolved or controlled within a reasonably short time. This is the sort of case about which the questions asked in the introduction to this paper were posed so hopelessly.

When a case of chronic, recurrent urticaria can be convincingly resolved, the cause is most likely to be a substance that is ordinarily harmless in its usual manner of action, and the pathogenetic mechanism by which it has become urticariogenic is allergic sensitization. Sometimes primary urticariogenic substances such as opium or atropine alkaloids are less subtle causes.

None of this is to say that a specific substance and an allergic or pharmacologic mechanism toward whealing can often or easily be uncovered. If, however, the cause and mechanism of all cases of chronic, recurrent urticaria and angioneurotic edema could be resolved, or especially if a true count were made of whatever cases are definitely resolved, the main mechanism would be found to be allergic sensitization, and the main allergens would distribute themselves in something of this order of frequency:

Drugs and simple chemicals encountered in foods	85%
Products emanating from foci of microbial infections and helminthic infestation	10%
Food proteins	5%

Up to recent years the ascription of the cause of urticaria to drugs to the degree stated would have seemed incredible. But with the modern increase in the use of synthetic drugs such as the sulfonamides and biological materials such as hormones and antibiotics, the number of cases of chronic urticaria traceable to such agents is forcing conviction. Few physicians of experience have not by now seen cases of urticaria arise under their very gaze during the administration of a course of penicillin or upon exhibition of a sulfonamide or of many old drugs such as iodides, acetylsalicylic acid, phenacetin and quinine.

Focal microbial infection and helminthic infestation as causes of

chronic urticaria are convincing in cases in which eradicable foci are indisputably found and sharp disappearance of the urticaria follows upon extirpation of the focus. Unfortunately the determination of the existence of such foci and the possibility of eradicating them are fraught with great difficulty. When, however, the determination is correct and the eradication perfect, urticaria that is surely related is bound to disappear.

Specific foods as a cause of chronic urticaria are, in my opinion, rare. But they do occur, and when a food is the cause of chronic urticaria, it is usually a solitary article, not a haphazard group of foods. Thus one may be sensitive to a single cereal or a nut, a vegetable, a fruit, a fish, a meat, a fowl, but not to a conglomeration of, say, chocolate and wheat and nuts and fish. Of course one may be sensitive to a single entity, more likely a simple chemical than a definable protein, which may be present in many natural foods (as iodine in fish, for example) or may be found in many different processed foods (as a preservative, for example), so that a broad spectrum of sensitization to many foods may be suggested, but the true situation is again sensitization to a single agent. If multiple sensitizations do occur, then some cases of urticaria are on the atopic basis and present the general difficulty of diagnosing and managing problems in atopy, which is another unhappy story.

SPECIAL TYPES OF URTICARIA

"Physical" Urticaria Resulting from Agencies Such as Mechanical Trauma (Stroke, Friction, Pressure), Heat, Cold, and Electromagnetic Energy (Limited Ultraviolet Light Ranges)

Urticarial dermographism is different from all other forms of urticaria in that the condition is patently caused by stroke or pressure, and in that the wheals take the precise geometric form of the stroke or pressure. The very title, "urticarial dermographism," implies the peculiar circumstance that the skin can be written upon in wheals. Truth to tell, all skin can be written upon in this manner if the stroke or pressure is hard enough, but the abnormality that merits the title is the condition evoked by an amount of stroke or pressure which is minor or encountered in average living, and does not ordinarily cause wheal-like edema in normal persons. Everybody would wheal under a whip lash, but only the person who exhibits urticarial dermographism suffers a wheal under a moderately firm stroke of a blunt instrument such as a tongue depressor, from a lover's pinch or upon the release of the pressure of a belt or girdle.

The possible mechanisms that have been conjectured to explain the condition are (1) excessive histamine release, (2) sensitivity to average amounts of histamine, and (3) specific, acquired sensitivity (allergy)

to autochthonous antigens arising from body-own proteins that are injured by the minor trauma of stroke or pressure. In the event of a whip lash it is credible that enough histamine may be released from tissue injury of such severity to cause whealing, since histamine inherently is pharmacodynamically and powerfully urticariogenic. One does not have to be allergically or in any other manner abnormally sensitive to histamine to respond with a wheal to critical concentrations of histamine. In the manner of stroking or pressing to elicit urticarial dermographism it is hard to imagine enough histamine production to effect its inherent action, because the same amount of trauma does not evoke the event in everyone, as it should if an urticariogenic amount of histamine is always produced in that manner. Nor is it proved that persons who ex-

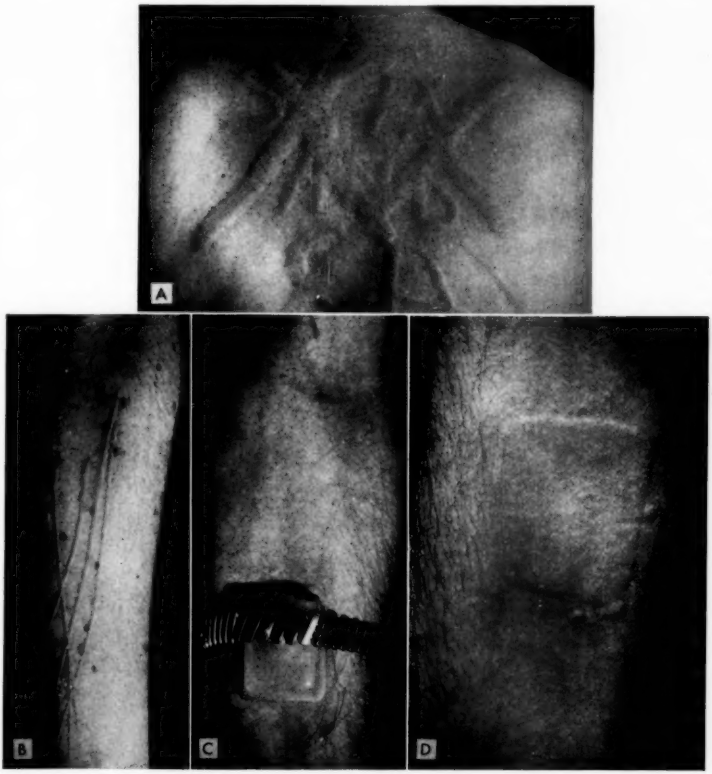

Fig. 21. "Physical" urticaria. *A* and *B*, Urticarial dermographism. *C*, Mode of eliciting an urticarial reaction to cold in a person sensitive to cold. *D*, The urticarial reaction to cold elicited in a person sensitive to cold by the method illustrated in *C*. (From the Collection of the Skin and Cancer Unit of the University Hospital of the New York University-Bellevue Medical Center.)

hibit urticarial dermographism are abnormally sensitive to less than critical amounts of histamine as an idiosyncrasy; they do not seem to respond differently from normals upon artificial introduction of histamine by injection.

One is left, then, with the possibility that urticarial dermographism is grounded in adventitious sensitization of some persons to body-own substances that are produced or released as antigens in all persons in response to light stroke or pressure. Support for the theory comes from some cases in which passive transferability of the phenomenon can be shown. It can sometimes be demonstrated that a stroke over a site in the skin of a recipient who is normal in this respect, but who has been prepared by injection in that skin site with serum from a donor with urticarial dermographism, will provoke a wheal. This means that the donor's serum contains antibodies which react with antigen, which is inevitably released in anyone by minor trauma. Further support for this interpretation comes from cases of urticaria caused by heat, cold and light in which the same phenomenon of passive transferability can also sometimes be demonstrated. In the instance of urticarial response to the shine on the skin of ultraviolet light, the wavelength range in particular cases is sharply limited, which suggests specificity of the evocative physical effect that equals the specificity of allergens required in the proof of the less imponderable allergic reactions.

"Papular" Urticaria Resulting from Venoms Injected by Stings and Bites of Insects and Metazoa of Other Orders or from Sensitization to Other of Their Products That Are Ordinarily Harmless

Bites and stings of insects and other creatures, or mere contact with some of them, may produce whealing of the customary sort or may result in pruritic papules that are different from ordinary hives in that the individual lesions tend to persist for longer periods (days rather than hours) than is usual for common wheals. Children are more susceptible to this type of metazoal assault, probably because they are less defensible, and are more responsive to it by production of edematous papules.

The title, "papular" urticaria, is not too distinctive, and in other times and places designations such as lichen urticatus, prurigo (mitis and ferox) and strophulus have been used to label conditions characterized by pruritic, transient or persisting papules. Differential diagnosis between wheals and papules caused by bites and stings and similar things of other cause is important because prognosis and management are so different. When the cause of a condition that could take the title of "papular" urticaria is surely not bites or stings, the subjects are usually of the atopic habitus, and the mechanism of such lesions is as recondite as is the rest of atopic dermatitis. They may be mere variants

of the cutaneous atopic complex and have nothing to do with being insect bait. On the other hand, there may be a more intimate relation between the wheals and papules of metazoal bites and stings and variant forms of atopic dermatitis. Recalling how readily atopic persons acquire sensitization that results in immediate (wheal) reactions, it may well be that such persons react with papules as a clinical variant of atopic dermatitis after they have been sensitized to insect products in the atopic manner and that they do this on many occasions, or on every occasion when they are bitten or stung. If this is true, then it is understandable why wheals and papules caused by metazoal bites and stings in some patients (the atopic) are more lasting and more difficult to abate than the average wheal or papule of the same cause in an ordinary (nonatopic) person, who may be responding merely to a primary urti-

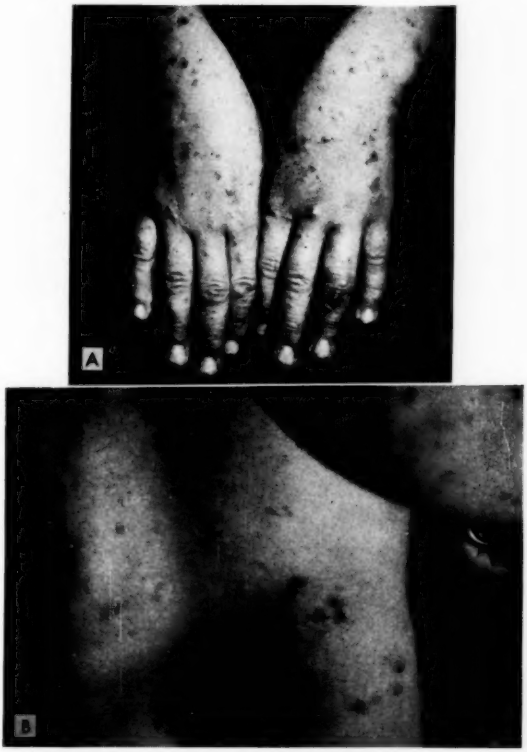

Fig. 22. "Papular" urticaria. This case is probably a variant form of atopic dermatitis. (From the Collection of the Skin and Cancer Unit of the University Hospital of the New York University-Bellevue Medical Center.)

cariogenic substance (the venom) with brief effect or by an antigen-antibody interaction of average, short duration.

"Cholinergic" Urticaria

"Cholinergic" urticaria appears as small, matchhead to pea-sized wheals which itch but moderately. The condition occurs in certain excitable persons under influences such as environmental heat, exercise or "emotion." It used to be thought that persons responding in this manner produced excessive amounts of acetylcholine (which, like histamine, or

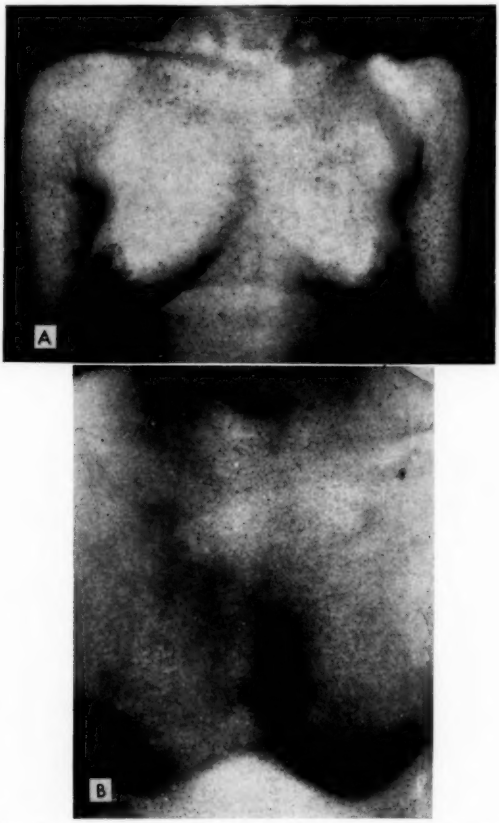

Fig. 23. "Cholinergic" urticaria. The small wheals of this type of urticaria do not photograph distinctly in black and white. (From the Collection of the Skin and Cancer Unit of the University Hospital of the New York University-Bellevue Medical Center.)

by virtue of liberating histamine, is inherently urticariogenic) until it was determined that they do not. Then it was found that they are abnormally reactive to average amounts of acetylcholine upon artificial introduction (not allergically hypersensitive, but somewhat more sensitive than "normal" persons who are merely sensitive, as is natural). But what accounts for this hypersensitivity, if not allergy? Well, it would appear that a deficiency of cholinesterase or failure of enzymatic destruction of acetylcholine by cholinesterase may be the answer. However all this may be, two conditions must conjoin to produce "cholinergic" urticaria: namely, heat and a person of proper quality with respect to acetylcholine metabolism. Let it be noted that heat is one of the critical factors and may arise from exercise and environment as readily as from psychologic excitement.

CAN WHEALING BE CAUSED PURELY BY A PSYCHOGENIC MECHANISM?

There is scarcely an article on urticaria—this one is an exception—that does not list psychologic difficulties among the prominent causes of acute and chronic, recurrent urticaria. And, after such listing, deep discussion of the matter is usually slurred or dropped. This is not satisfactory. The question of what precisely causes a disease is complicated enough, and when the psyche is implicated in disease causation, complexity is compounded. It is true that things are more complicated than most persons think, but it behooves us not to surmount complexity by ignoring it. Let us try to explore what we mean by "cause" of disease and how the psyche can be inserted into a concept of disease causation.

If one took a simple vote on it, most physicians would surely say that psychic difficulties can "cause" hives. If one presses the issue for more proof than a voting opinion, it is usually given in the form of a vaguely remembered case history of a patient who stated that he or she has or had hives every time a domestic, financial, amorous or career catastrophe is or was threatened or a crisis of these sorts occurs or occurred. The documentation of such cases in terms of time correspondence of emotional upheaval and onset and duration of urticaria, and inevitable repetition on every occasion is never good. The doctor cannot assert that he observed every or even several such episodes; usually merely the patient's assertion is taken as scientific verity. Rigorous cross examination for episodes of emotional disturbances of proper quality (an immeasurable item at best) that were not attended by hives and inquiry for more common causes of urticaria such as the coincidental taking of drugs for sedation or tranquilization at periods of emotional stress are not reported. The eagerness to "latch on" to something that can be construed as cause usually stops investigation of other causes which are more likely, though equally difficult to prove. Moreover, it is more com-

fortable to accept a mystique than to remain in agnosticism. It's a common human failing.

One must digress for a moment to examine what we mean by the cause of a disease. Elsewhere* I have written as follows:

> It is common to think of the causes of diseases in terms of single agents or unitary mechanisms. In many conditions it is possible to recognize single or quintessential causes, e.g., microorganisms in infectious diseases, and physical force in traumatic effects, but upon analysis it always becomes apparent that a train of circumstances must attend a cause before it becomes operative, and once operative many more things may happen to abet or inhibit cause, add or subtract from it, or modify it in tangential directions. That is to say, there may be indispensable causes or mechanisms without which disease will not occur, but their simple presence does not make disease inevitable without critical factors of sufficiency in amount and intensity or without other less obvious factors. Or, to put it in another way, what could be a cause may or may not induce disease, depending on the concurrence of many adjuvant or preventive factors. Then, disease finally induced, its quality and quantity may be varied, depending on conditions and circumstances not particularly related to prime cause.

Now, in the matter of mind and disease, the question is: Can the vague thing called "emotion," or whatever else constitutes a deviation from "normal" mentality, in and of itself bring forth definable disease pictures in other organs or the system as a whole? It is well known that things going on in the mind can, by direct neurologic connection and by the biochemistry involved in neural action, cause transient or moderately sustained, frequent or occasional, physiologic alterations in other organs that are far from the mean of homeostasis. For example, shame can cause vasodilatation to a degree that can be read in the skin as erythema, and fright can cause vasoconstriction to a degree that can be read as pallor. Comparable effects in gastrointestinal, cardiac, pulmonary and other organ function can be appreciated. If such things are construed as expressions of disease, then most of us are sick most of the time. This is not a fruitful way of looking at psychosomatic interaction. It may be, however, that frequent and sustained wide swings in physiology can promote (or abate) certain disease processes. The critical question for us in the present context is whether a mental state of proper quality can cause blood vessel dilatation and increase in blood vessel permeability directly by efferent neural stimulation or through influence upon other organs (endocrines?) to a degree that will permit passage of plasma fluid into tissues in the common urticarial manner.

Thus, can one conceive and prove a sequence of physiologic alterations to the point of whealing from mental disturbance? The major psychoses—schizophrenia, manic depressive psychosis, and others—are not notable for concomitant urticaria. It is lesser psychopathy that is always implicated in this connection. It seems so attractive to imagine that if mental distress can cause one to blush or faint, to breathe heavily

* M. Leider: *Practical Pediatric Dermatology*. St. Louis, C. V. Mosby Company, 1956, p. 97.

or catch the breath, to lose control of bladder and rectum, to race or slow the heart and to mess up comfortable function in many more ways, it ought to be able to cause a seemingly simple reaction such as whealing. But how? Can one show that certain qualities or intensities of psychic activity result in the production of enough histamine, acetylcholine, serotonin or other vasodilating substances to do this? Or can one show that in the grip of psychic difficulty some persons are more exquisitely sensitive to these substances? Nothing of this sort has been proved to obtain for acute and chronic, recurrent urticaria.

It is only in the variety of urticaria called "cholinergic" that anything suggestive of a direct connection between emotion and a type of whealing has been adduced. It has been credibly observed that some persons under mental excitement repeatedly break out into small hives, usually on the upper chest. But they do the same thing during physical exercise and in quiet circumstances under environmental heat. It seems that heat and a quality of person are the critical factors in this event. So it may be that mental excitement of sorts results in a rise of body heat from increased metabolism, and in some persons for reasons uncertain (it may be transient failure of deactivation of acetylcholine by cholinesterase) this leads to a certain type of whealing. "Cholinergic" urticaria may be a special case in which psychologic activity, among other things, may initiate circumstances that eventuate in whealing of a special sort. But "cholinergic" urticaria is not the same as acute and chronic, recurrent urticaria, which are the types about which the issue generally revolves. There is no evidence even as tenuous as that for "cholinergic" urticaria that psychologic states can cause banal urticaria.

MANAGEMENT OF THE URTICARIAS

Treatment of the urticarias divides itself obviously into nonspecific measures directed at the pathogenetic mechanism of whealing and symptomatic relief of itching, and specific elimination of discoverable cause. Discovery and elimination of cause are no doubt the best treatment, but not, alas, frequently possible as yet. Nevertheless, a combination of occasional discovery and elimination of cause by ingenious and tireless investigation plus the practice of versatile palliative measures is highly rewarding. We now consider some of the possibilities of effective therapy in the different types of urticaria.

Acute urticaria and angioneurotic edema of the average type, i.e., an episode destined to last but a few days, may be instantly controlled for a short time by one or more intracutaneous (rather than subcutaneous) injections of 0.2 cc. of a 1:1000 solution of epinephrine. This is good practice if the presenting attack is severe. After injection of epinephrine if need be, any of many antihistaminic agents will usually maintain con-

trol until spontaneous cessation of the condition occurs. For infants the elixirs of Benadryl or Pyribenzamine in doses of 10 mg. (1 teaspoonful) every 3 to 4 hours, and for older children 20 mg. (2 teaspoonfuls) every 4 hours, ought to be adequate. The soporific side effect of these agents is an advantage in small children; in older subjects it may be undesirable. For youngsters who have learned or can be taught to swallow tablets, Chlor-Trimeton in doses of 2 to 4 mg. every 4 to 6 hours or Perazil in doses of 12.50 to 25 mg. or many other drugs of the class are easy forms of medication. The trick is to find one that suppresses whealing and does not induce sleepiness, if this is interfering with school or other important activities.

The old-fashioned routine prescription of an initial purge is not advised. If gastroenteritis is concomitant with the urticaria and its quality is such as to make violent evacuation a reasonable thing to do, then let it be done. Similarly, variation of diet, except for what is dictated by incidental illness, is also not advised. The traditional sweeping elimination of foods that have a false reputation of being common causes of urticaria (fish, nuts, berries, chocolate, and so on) is irrational unless there is clear indication that a particular one is at fault.

If acute urticaria takes the form of angioneurotic edema and if a region such as the tongue or pharynx is involved, heroic emergency measures such as tracheotomy may be required because whealing in these sites may cause suffocation. Of the drugs that may save life in such a situation, intracutaneously administered epinephrine, intravenously administered antihistaminics, intramuscularly administered cortisone or intravenously administered ACTH are the most likely agents to do this.

The topical treatment of urticaria is not brilliant, but whatever diversion from the sensation of itching can be obtained from lotions containing menthol and phenol is worth while. The following is a representative prescription for the purpose:

℞ Menthol ..... ⅛%
Phenol ..... ¼%
Magnesium carbonate, heavy 10%
Talcum 10%
Zinc oxide 10%
Olive oil 5%
Lime water, q.s. ad 240
S. Apply freely and frequently with a paint brush.

Chronic recurrent urticaria and angioneurotic edema may be manageable palliatively in the manner of acute urticaria with epinephrine when necessary in emergency or for isolated severe episodes, with cortisone and/or ACTH, if effective, in prolonged attacks and best of all with an antihistaminic that is suppressive. Sometimes control by such measures is all that is possible and may in the long run be controlling

until spontaneous cessation occurs for fortuitous, if unknown, reasons. But chronic urticaria and angioneurotic edema lend themselves more than the other urticarias to definitive resolution of cause—not always, not frequently, but still sometimes. And when cause is discovered, a long-enduring case can be quickly and gratifyingly cured—if that cause can be eliminated and avoided.

In accordance with our expressed opinion that the order of frequency of cause of chronic urticaria is drugs (85 per cent), focal infection and infestation (10 per cent) and foods (5 per cent), the most profitable direction of search for cause is in exposure to drugs and simple chemicals that are taken by mouth, inhaled, instilled, administered by injection or obtained from occult sources such as processed foods. In order to test and prove a drug cause, the first thing to do is to interdict the taking of all drugs that may be a current habit and not strictly needed (vitamins, "sleeping pills," "reducing pills," nose drops, and others), and then to enter upon a careful and thorough inquiry to discover all possible administrations of drugs. This inquiry is not a simple matter of asking the patient whether drugs are being taken. The usual response will be "No," an honest statement which is almost always misleading and untrue, because it would be a phenomenon worth reporting to find a person in modern times who does not regularly or irregularly, needfully and needlessly, take drugs or simple chemicals, either consciously or unconsciously. Most people do not think of materials such as vitamins or analgesics as drugs or as things worth reporting.

My routine for taking a systematic drug history is first to ask the general question as to whether drugs are being taken for any condition other than for the hives. Positive answers are duly noted, and if the answer is "No"—even if convincingly uttered and reasserted by the patient—detailed questioning is begun. The best place to begin digging for more drug possibilities is to take the patient back to the beginning of the hives (months and sometimes years ago). It will sometimes be found that chronic recurrent urticaria began after a simple illness such as the common cold or a more serious condition such as a cardiopathy, a gastroenteropathy or a severe infection that required medication by mouth or parenterally for a short or long time. Then by obtaining with the patient's and pharmacist's cooperation the exact prescriptions, a wealth of drug possibilities may be uncovered. If this avenue of investigation is not productive, another tack is to question systematically about medication for common symptoms. Analgesics for headaches and dysmenorrhea, drops for eye, ear and nose complaints, medicines for gastric distress, cramps and constipation, sedatives and tranquilizers for insomnia and "nervousness," antiseptics such as mouth washes and douche materials, and so on, must be inquired about. Productive or not, another trick to discover drugs that may be or may have been taken and are

honestly forgotten is to have the patient bring in an inventory of the family medicine cabinet and other stores of active and left-over drug remnants. Survey of such lists sometimes reveals or recalls possibilities. Finally, when all such detective work is done, if palpable drug culprits are not uncovered, repeated cross examinations over and over again may be finally revealing. If one were to list the drugs most likely at fault, the following would probably be most frequent statistically: penicillin, sulfonamides, salicylates, iodides, barbiturates, phenacetin, quinine and codeine. Besides these, all other drugs are suspect and at times may be actual causes in particular cases.

If a drug possibility of some convincing quality is uncovered, strict avoidance, *if possible*, ought to be quickly curative *if truly causative*. When, in spite of conviction and in spite of apparently honest avoidance of the probable causative drug, the urticaria still persists, occult sources of drug ingestion must be considered and sought. For example, a patient may truly be sensitive to aspirin, may avoid taking aspirin as aspirin, but may not realize, if not told expressly, that other salicylates such as sodium salicylate and methyl salicylate (oil of wintergreen) in proprietary analgesic mixtures and in balms may be a source of unwitting exposure. As another example, urticarial sensitization and provocation by iodine may persist, in spite of apparent avoidance of a specific medication such as potassium iodide, by virtue of exposure from topical application of tincture of iodine (iodine is readily absorbed by the skin), from iodized table salt, iodized tooth pastes or iodine-containing foods such as shell sea foods (oysters, lobsters, shrimp, clams, crabmeat).

If the avenue of drug investigation is barren or ends in a blind alley, focal infection and infestation offer the next most rewarding area of etiologic search. In children the teeth, tonsils, sinuses and middle ear are likely places of bacterial focal infections, and the intestinal tract is about the only site of helminthic focal infestation. The fact of focal bacterial infection is sometimes a shaky clinical judgment, but helminthic infestation can be proved by stool examination. Discovery of a likely focus of either sort merits extirpation by whatever means could be efficacious: surgery and/or antibiotic therapy for teeth, tonsils, sinuses and middle ear disease; anthelmintics for definitively proved helminthiasis. If such a focus is truly the cause of urticaria in a given case, absolute removal should cure absolutely.

Finally, if both drug causes and focal infection or infestation are not to be found, attention may be turned to food as a rare possibility. In my experience, if the patient himself cannot pinpointedly name the precise food, the likelihood of food cause is remote. There is something about sensitization to a solitary dietary item that makes it clear to the patient. If the patient guesses at a lot of foods or designates an entire

category such as citrus fruits or all meats, or on one occasion implicates an item because he recently (why, just the other night!) ate it (although dozens of other items were eaten at the same time and are not deemed worth mentioning) and on another occasion accuses something else again, then a food is probably not the cause. That is just foolish guessing. But when the patient specifies one food, say green peas, not legumes in general, but only green peas and nothing else, then the accusation is credible. The food mentioned is probably the culprit; it need not be confirmed by testing; it had better be traced in all its culinary disguises, and avoided like poison, indeed!

If proof of a food sensitization cannot be had, there is no point in prohibiting a whole series of foods in an omnibus way because they have a reputation, never proved by true experience, to be notoriously urticariogenic. Probably more cases of chronic urticaria have been caused by sensitization to benzoic acid as a preservative of strawberry jams than by strawberries as a food. Probably more cases of chronic urticaria have been caused by sensitization to iodine in shell sea food and other fish than have been caused by fish protein. Probably more cases have been caused by sensitization to other simple chemicals such as antimolds, wheat-aging agents or substances such as sodium nitrate used in meat corning than have been caused by the characteristic proteins of the foods that contain these chemical materials.

If a patient should be truly sensitive to many foods of entirely different types and really wheals from their ingestion, then the problem is probably one of atopy. Attempt to investigate such cases by skin tests (scratch or intradermal) is not frequently—if ever—productive. Such testing may be hazardous and is frequently misleading because the tests do not and cannot possibly include all food possibilities. Rarely are such test readings unequivocal, and it is more than possible that what one tests with in the form of commercially prepared antigens does not correspond at all with the particular protein or nonprotein allergen that may be truly causative. Positive tests of this sort are more likely to be indicative of the atopic habitus than revelatory of causative possibilities. Moreover, if skin testing of this sort with common food allergens is practiced on the same atopic patient at, say, quarterly intervals (every three months), different patterns of positive reactions may be obtained. Under such circumstances the logic of cure by elimination of foods may ultimately require starvation, which, carried to extreme, could cure everything.

The use of "elimination diets" for diagnosis and cure is another routine of uncertain merit. Rarely can good elimination routines be carried out, and rarely is the practice of a severely restricted diet less of a bother than the urticaria. It would be interesting to know exactly how often a causative food is actually discovered in this way. Figures, anybody?

In short, it is my opinion that foods are rare causes of chronic urticaria, that when a particular food is at fault, the patient knows it from convincing circumstantial evidence, and that when hives persist in spite of strict avoidance of obvious sources of a food truly at fault, the problem comes to one of occult exposure. For example, urticaria truly caused by egg (white or yolk) would tend to keep on because egg is widely used in many processed foods. Corn products are in the same class. Another food such as a bean would seem to be more easily avoidable, but, again, contamination from an insufficiently washed restaurant plate might be a source of occult ingestion. Urticaria caused by food is usually exquisite and requires but the minutest amount of antigen. Cure of urticaria of food cause is assured if the food can be avoided. Failing the possibility of complete and everlasting avoidance, acute episodes of urticaria may be expected and have to be treated as short-term emergencies.

"Physical" urticaria caused by stroke or pressure, light, heat and cold, and "cholinergic" urticaria are managed on principles of avoidance of provocative events and by drugs that interfere with the pathophysiology of whealing. Thus friction, pressure, actinic radiation, excessive warmth of internal or external origin, excessive cold, unnecessary physical activity and "emotional" upsets may be avoidable if it is explained to the patient how they may be avoided in all circumstances, some of which may not be obvious. In addition, antihistaminics in doses adequate to control whatever whealing cannot be prevented by avoidance of the physical noxae can be given with good effect. Another measure advised for urticarial dermographism is daily showers with a thorough scrubbing of the skin with a moderately stiff brush. On theory, and to some extent in effect, a temporary exhaustion of the whealing phenomenon may thus be achieved. Both urticarial dermographism and "cholinergic" urticaria are unpredictable in duration, but there is a tendency to spontaneous remission, sometimes in a reasonable time (months) and surely at long last (years).

"Papular" urticaria, when it is really a matter of insect bites, is a problem in zoologic sanitation. Screening of windows and disinfestation with DDT of the immediate environment of the home (beds, house furniture, gardens) may end the problem. When papular urticaria is an atopic expression, then more intensive and difficult treatment with topical and systemic agents will be required. In the latter circumstance, in addition to topical antipruritic agents (see prescription, p. 838), systemic antihistaminics and even corticosteroids or ACTH in the severest forms (prurigo ferox) may be necessary.

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RHUS DERMATITIS

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Contact with two colorful and innocuous-seeming plants, poison ivy (*Rhus radicans*) and poison oak (*Rhus toxicodendron*), is the single most common cause of allergic reactions in America. Millions are afflicted with Rhus dermatitis each year. Over half of these are children. Obviously a disease of this magnitude should be well described and understood by all practitioners of medicine, especially those who deal with diseases of children. But this is not the case. As indicated elsewhere,[6] misconceptions about Rhus dermatitis are rife among physicians and laymen alike. Few have concerned themselves with the vagaries of this annoying dermatitis, and fact and fantasy are constantly confounded. Kligman's recent, thorough study of the problem clarifies much of this confusion.[17]

In this review I will discuss (1) certain basic aspects of Rhus dermatitis pertinent to the practice of pediatrics, and (2) treatment as viewed by a dermatologist.

BASIC CONSIDERATIONS

Rhus dermatitis is an allergic contact dermatitis caused by intimate exposure to plants of the genus Rhus. It is a form of delayed hypersensitivity closely akin to, if not immunologically identical with, tuberculin hypersensitivity. Poison oak and poison ivy leaves produce similar eruptions in the same person. Since clinically we cannot distinguish the two rashes,[17] we can anticipate that chemically the same allergens will be isolated in both plants. Only poison ivy has been analyzed to date.[23, 46]

Rhus hypersensitivity must be acquired. Infants are not born with it, but, as Straus[44] pointed out, they are easily sensitized. We have

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sensitized 75 per cent of 24 children between the ages of 6 and 24 months by applying 0.25 ml. of a 1:100 acetone solution of pentadecyl catechol (P.D.C.), a synthetic Rhus allergen,[3] as an open patch test.[7] Using the same technique, Kligman[17] sensitized 85 per cent of 34 children aged 2 to 8 years. Despite their obvious susceptibility, most children remain free of the dermatitis until the age of six to eight years. Lack of exposure likely explains this observation.

The incidence of clinical Rhus sensitivity in the general population in America is about 50 per cent,[4, 17, 20, 41, 42] with the highest percentage of reactors in the younger age groups.[17] On the other hand, between 75 and 85 per cent of adults will react to 1:100 pentadecyl catechol.[7, 17] This means that a large reservoir of subclinical reactors exists in the population and that nearly everyone acquires a sensitivity to Rhus, either clinical or subclinical. Europeans, who normally are never exposed to these allergens, are readily sensitized experimentally.[1, 40] Clearly, Rhus allergens are among the most potent sensitizers known!

There are a few negative reactors who cannot be sensitized even after exposure to massive amounts of a very irritating 25 per cent P.D.C. solution.[7, 17] However, a single intradermal injection of a relatively small number of leukocytes from a sensitive donor is sufficient to induce a generalized sensitivity in these hardy souls.[8] Sensitivity is not so easily transferred to children.[8] The explanation for this phenomenon is obscure, but we can assume that lack of exposure is not responsible for the behavior of our negative adults. It seems that previous exposure to Rhus allergens has engendered a tolerance rather than an intolerance. The concept that the initial contact with chemicals and drugs can induce tolerance as well as intolerance is an important one that necessitates further study.

Another peculiar observation is that Rhus dermatitis is primarily an American disease despite the widespread distribution in nature of closely related, cross-reacting allergens. Orientals, for instance, who are born and raised in the Orient normally are not afflicted with the disease even though Rhus or related allergens abound there to plague the unfortunate American traveler.[17] Once again we have no suitable explanation. Some workers have suggested that early exposure to related allergens inures one to Rhus,[5] but evidence on this point is controversial,[17] and the issue remains unsettled. On the other hand, certain facts about racial susceptibility are clear. American Indians, contrary to folklore, have no natural immunity to Rhus dermatitis,[4] and Negroes react less to contact allergens than do whites.[9–11, 17]

CLINICAL CONSIDERATIONS

Rhus dermatitis is acquired only through contact with the Rhus allergens contained in the oily sap of the plant. No toxic gases emanate

from the weed; the allergens are not volatile. However, smoke carrying particles of the plant can and often does disseminate the disease. More obscure transmitters are intermediary fomites such as clothing, tools or animals. The allergens retain their potency for months when dry, but are rapidly inactivated when wet. Thus one may acquire the dermatitis without directly touching the growth. Recognition of this possibility may prove invaluable in diagnosing the cause of certain acute dermatoses.

The reaction time, or time after exposure before the rash appears, is variable, depending on the degree of sensitivity and the extent of exposure. Very sensitive persons may react within 6 hours after contact, while less sensitive persons may not have a rash for a week or 10 days. Even more important, the reaction time varies at different sites in the same person. Areas of most intense exposure tend to react before those of lesser contact. This frequently but not invariably results in the appearance of a spreading rash which usually is incorrectly ascribed to the effect of blister fluid leaking onto normal skin. Blister fluid contains no active allergen,[28] but if residual allergen remains free on the skin, it can be spread by scratching or by means of several agencies, including sweat and blister fluid. Repeated exposure to unrecognized and contaminated fomites may also give the appearance of an extending dermatitis and often accounts for prolonged bouts of Rhus dermatitis in very sensitive sufferers.

In the eastern United States the incidence of Rhus dermatitis varies greatly with the season, reaching a peak in springtime. The popular but false assumption that variations in potency of the sap account for this finding has been dealt with by Kligman.[17] He found no real differences in reactions to leaves plucked at various times throughout the year. He emphasized that more persons make their communion with nature at this time, unwarily crushing the tender spring leaves with an abandonment not seen later. In the more temperate climes of the West the call to the outdoors never abates, and we see Rhus dermatitis all year round. However, the severity of the dermatitis clearly varies with the weather. Heat aggravates the reaction, while cold diminishes it. As a proof we placed three patches of P.D.C. on the same arm of four subjects and then covered one with a hot water bottle and one with an ice pack, leaving the middle patch untreated. The packs were maintained respectively hot and cold for seven hours a day. Two days later, as expected, the heat-treated sites were found more reactive and the cold-exposed areas less reactive than the control.[7]

Although, clinically, Rhus dermatitis characteristically presents as a vesicular dermatitis, it must be recalled that the earliest and weakest reactions appear as simple erythema. The first visible reaction histologically is a dilatation of the superficial blood vessels of the skin with a

perivascular accumulation of round cells.[2, 26] Only later does the epidermis become involved in the process of vesiculation. Massive edema of the affected part, another evidence of vascular damage, occurs in more severe reactions. Even urticaria is seen in some persons. But the suggestion that an immediate type of hypersensitivity may coexist with the delayed type in Rhus sensitivity[17] is as yet unproved, and anaphylactoid reactions have never been seen in man.

Other dermatitic manifestations of Rhus sensitivity include dsyhidrotic vesicles on the hands and feet and a disseminated maculopapular erythematous eruption seen rarely in very severe cases. The lesions of Rhus dermatitis generally heal with slight to moderate hyperpigmentation, but hypopigmentation is also seen at times.[25]

Aside from extreme malaise, irritability and a low grade fever in severe cases, systemic symptoms are not expected. A leukocytosis ranging from 10,000 to 20,000 cells per cubic millimeter with slight eosinophilia may be noted, but albuminuria is not a concomitant of Rhus dermatitis.[17, 47] A few instances of renal disease following Rhus dermatitis have been reported,[29, 30, 32] but it is not at all certain that the one caused the other. Aside from the possibility of mere coincidence, we must consider the likelihood that a secondary bacterial infection of the dermatitis occurred which then triggered off the renal disease.[29]

TREATMENT

The chief aim in treatment is to relieve pruritus. The disease itself runs a self-limited course, and the vesicles, although a nuisance, do not exasperate the patient as pruritus does. Unfortunately, current treatment of pruritus is inept. Topical therapy with calamine lotion or any bland lotion or cream is as effective as more expensive, highly advertised preparations. Even the potent topical corticosteroids have "flunked" a double blind test.[33] In fact, we have found no advantage to using these preparations in acute contact dermatitis. On the other hand, in chronic dermatitis accompanied by thickening, lichenification and scaling, topical corticosteroids are of unquestioned value. Whether triamcinolone acetonide* is more effective than others remains to be seen.

The ideal treatment creates a salubrious environment in which damaged skin can heal. Harsh and irritating medicaments contravene this principle. Complete rest in bed is surprisingly effective. Soothing lotions and high doses of aspirin or sedatives are also useful. Although histamine is unquestionably released in the skin during contact dermatitis,[13, 16] antihistaminics are ineffectual except as poor sedatives. This conservative form of treatment is palliative, not suppressive, and is satisfactory for mild and moderate cases of Rhus dermatitis.

* Kenalog, Squibb; Aristocort Acetonide, Lederle.

In extreme cases with great discomfort and disability systemic therapy with corticotropin or one of the corticosteroids is indicated. These drugs have revolutionized the treatment of allergic contact dermatitis. They suppress the inflammatory response. Edema melts away; vesiculation is reduced. But the disease is not cured; it must run its course, and therapy must be continued until it is quiescent. This usually requires one to two weeks. I generally start with the equivalent of 200 mg. daily of hydrocortisone or 80 units of ACTH-Gel in divided doses, gradually reducing the dose over 7 to 14 days, according to the response of the patient. A flare-up of the reaction will occur if the drug is removed too quickly. An occasional patient requires even larger doses. Complete suppression of the disease should not be expected. Sulzberger et al.[45] have shown that oral cortisone reduces but does not completely inhibit the contact patch test. So it is with the disease. Although edema and discomfort are controlled, some vesiculation and erythema may persist. Patients with primarily a vesicular response may be resistant to this therapy. I therefore reserve corticosteroids for severe cases, even though these drugs are usually safe in the short courses used.

One other form of treatment must be mentioned, only to be condemned. Injection of Rhus allergen during the acute dermatitis is irrational and useless and may be harmful. Kligman has considered these criticisms in some detail.[17] Suffice it here to say that in general the medical concept of fighting fire with fire has fallen into disrepute. Our experience in the experimental prophylaxis of Rhus further attests to the spuriousness of the concept. We gave a number of subjects intramuscular injections of large doses of allergen (0.1 ml. of a 10 per cent suspension) during the height of a dermatitic reaction. In no case was the course of the disease shortened. Usually nothing happened; but in some the dermatitis was aggravated, and in a few it became severe enough to warrant hospitalization. Unhappily, antigen therapy continues as a popular treatment in some areas and is even condoned[14, 27] despite warnings to the contrary by most manufacturers of Rhus extracts. These commercial products fortunately are diluted enough (usually to 1 to 2 per cent) to minimize the danger of such reactions, but intelligent management of a self-resolving dermatitis should not allow for such therapy.

PROPHYLAXIS

Prevention of Rhus dermatitis has received much attention, and deservedly so. Many methods and treatments have been devised to destroy the plant or protect the patient. None is wholly effective. The only infallible method is complete avoidance of Rhus or related allergens, and, as noted before, this can prove nearly impossible.

Destruction of the plant by physical or chemical means has two main disadvantages: (1) eradication cannot be assured, owing to the hardiness of the weed, and (2) uncleared land nearby serves as a source of indirect contact through the medium of fomites such as curious pets and children.

Protection of the patient by external treatment has proved equally unsatisfactory. Barrier creams not only are impractical, but also have little prophylactic value.[17] Topical detoxicants, though theoretically attractive, have failed clinically. Even the time-honored remedy of thoroughly washing after exposure has been discredited. In controlled studies Kligman[17] has shown that washing within 5 to 10 minutes of contact will not prevent a severe dermatitis in highly sensitive persons. Furthermore, washing may spread the allergen.

Systemic Prophylaxis

The central questions here are: Can a person be desensitized by administration of Rhus allergens, and, if so, is desensitization practical? An affirmative answer, of course, would have tremendous significance for millions of victims of Rhus dermatitis. It goes without saying that more has been written on this subject than on any other phase of Rhus dermatitis. Fantastic claims of success have been countered with outraged cries of failure. A general survey of the literature leaves one confused and disheartened. Even the A.M.A. Council on Pharmacy and Chemistry has failed to resolve the problem.[43] However, selective reading reveals that critical minds have been at work, and all is not lost. In the early 1940's Shelmire,[34–36] using a crude plant extract (oleoresin) and quantitative patch tests, showed that, though desensitization was not feasible, some reduction in sensitivity (hyposensitization) did result after administration of large amounts of allergen. He also emphasized the variable potency of extracts and their instability.[36] Furthermore, many commercial extracts have been found inactive or very weakly antigenic.[7, 15, 17] For these reasons, and because Shelmire also emphasized the toxic effects of Rhus oleoresin,[37, 38] most dermatologists have avoided Rhus hyposensitization.

A resurgence of interest has followed Kligman's detailed study of the problem.[18] Using strictly controlled quantitative patch tests with pentadecyl catechol (P.D.C.), a fairly stable, synthetic Rhus allergen, he has confirmed the fact that a limited degree of hyposensitization is attainable patch testwise and that the clinical protection afforded these patients consists in (1) milder attacks, (2) briefer duration, and (3) less dissemination of the dermatitis. Any active Rhus allergen, the crude oleoresin or P.D.C., can be used. Even a related allergen, Cardol, the oil of the cashew nut shell, is effective.[19] However, in contrast to most

authors who favor the use of a few milligrams of allergen, he, like Shelmire, found that massive doses must be administered—2 to 3 gm. of oleoresin, and 3 to 4 gm. of P.D.C. or Cardol. To achieve hyposensitization requires administration of large amounts of active allergen over a long time. Naturally the hazard of untoward reactions is considerable, but not prohibitive. Furthermore, hyposensitization is temporary, and sensitivity soon returns once treatment is discontinued. This means that a maintenance dose must be taken continuously and that single courses of treatment are without merit.

This picture is bleak compared to the popular version, which insists that a few injections of relatively impotent allergen will suffice for protection over a season, or even indefinitely. Nevertheless, clear indications exist for prophylactic Rhus hyposensitization. The child whose normal development is impeded by an intense, incapacitating Rhus sensitivity can be helped. In deciding whether or not to utilize the technique one should bear in mind that (1) children tolerate the procedure much better than adults; untoward reactions are fewer and milder; and (2) after the age of 20 or so reactivity will tend to lessen,[17] and treatment may be stopped.

As for the method of administration, we now consider intramuscular hyposensitization impractical and prefer oral administration of a 10 per cent solution in alcohol, with the addition of a wetting agent to increase absorption. Any active allergen can be used. Rhus oleoresin* and Cardol† are or will be available. The material is given carefully in a dropwise fashion in a full glass of water, stirred and drunk through a straw to prevent allergenic contamination of the lips. The dose is gradually increased until 3000 mg. (30 ml. of a 10 per cent solution) have been taken. The course usually requires three to eight months, depending on the patient's tolerance.

A suggested dosage schedule is as follows:

First week:	1 drop daily
Second week:	2 drops daily, in 2 divided doses
Third week:	3 drops daily, in 2 divided doses
Fourth week:	4 drops daily, in 2 divided doses
Fifth week:	5 drops daily, in 2 divided doses

After that the dose is increased 1 drop every 2 or 3 days until a daily total of 30 drops is reached. This is continued until a 30-ml. bottle is emptied, and then the patient is placed on a maintenance dose of 15 drops a day as a single dose in water.

Intolerance is first evidenced by pruritus, usually occurring on the arms or about the face and occasionally elsewhere. This symptom is an indication to reduce the dose by one drop and remain there until

* The most reliable oleoresin is supplied by Graham Laboratories, Dallas, Texas.

† Ingram Laboratories, San Francisco, will supply Cardol commercially.

the pruritus has subsided. Then the dose is increased again. By this stop-and-start method the patient's tolerance to Rhus is gradually built up.

Other reactions include a maculopapular rash in the areas of pruritus, flare-ups of sites of previous Rhus dermatitis, dyshidrosis and uncommonly urticaria. In general, pruritus ani is not a problem with the alcoholic solutions, although it occurred frequently with oily preparations. However, some patients excrete free allergen in their urine which can cause distressing eruptions. This difficulty usually is averted by giving the allergen more frequently, three or four times a day, in smaller amounts. If not, corticosteroids may have to be given for one to two weeks while the dose of allergen is raised and until some tolerance has developed.[18] Other unusual reactions are detailed by Kligman.[18] The course spans three to eight months and clearly is not a trivial procedure.

Another Rhus extract has recently become available. It is an alum-precipitated pyridine extract* that is supposed to lack toxicity. Kligman found it useless by intramuscular injection.[18] Langs et al.[21, 22] have reported great success in oral hyposensitization. In our laboratory oral use of the drug has resulted in some untoward reactions similar to those noted above, and a patch test with the crushed tablet is capable of eliciting a dermatitis in highly sensitive persons. Apparently the extract is active and therefore should induce hyposensitization. However, its exact status is still unknown, and unfortunately the drug has been released for general usage before solid recommendations as to dosage schedule, amount required, over-all toxicity, and so on, can be given.

Other Methods of Desensitization

Finally it should be noted that a severe bout of Rhus dermatitis may leave the patient immune to further attacks for variable periods of time. In experiments reported elsewhere[12] we have shown that repeated epicutaneous allergenic "shocks" can specifically desensitize a person. This finding agrees with experience in industry where workers handling allergenic chemicals become hardened or desensitized.[31] However, clinical application of this principle to Rhus dermatitis, with one possible exception,[24] has proved impractical.[18, 39]

SUMMARY

A great deal is known about the immunobiology of Rhus dermatitis. Superstition and folklore no longer should dictate our attitudes toward the problem. Facts are at hand to answer most questions.

* Aqua Ivy, supplied by Syntex Chemical Company, Inc., New York, N.Y.

Treatment should be geared to the understanding that Rhus dermatitis is a self-healing process and that our treatment of pruritus, the bane of the disease, is unsatisfactory.

Prophylaxis by immunologic means is possible, but not simple.

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SKIN TESTING FOR FOOD SENSITIVITY

Its Clinical Significance

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It has been correctly stated, by many of our foremost leaders in the field of allergy, that a good allergic history is by far the most rewarding procedure in the evaluation of an allergic problem. One does not dare to challenge this concept. However, even a so-called positive food history, which usually is supplied by confused and discouraged parents, does not always establish with finality the presence of clinical sensitization. Also, skin testing frequently fails us when food sensitization is known to be present, and on other occasions positive food tests may erroneously point to nonexisting food allergy. Sherman and Kessler[8] explain "the relatively greater incidence of false positive skin reactions to foods than to inhaled allergens" by the fact that whereas inhalants "come into direct contact with the sensitized tissues, food allergens are altered by cooking, by digestion and metabolism before reaching the shock organ through the circulation." As will be shown later on, in spite of its limitations the food test, if properly performed and correctly interpreted, may well be of considerable help in clarifying certain clinical situations.

The importance of properly evaluating the food test is clear. If it is correctly interpreted, a child will not be deprived of foods needed for growth and development. At the same time, whenever a food test is positive in a child with an allergic disease, especially if the reaction is a large one, it is mandatory that we determine by clinical demonstration whether the food in question is causing symptoms. That some positive skin reactions to food have no clinical significance is no valid reason for disregarding them altogether.

SKIN REACTIONS TO FOOD IN INFANTS UNDER TWO YEARS OF AGE

Positive skin reactions to food do occur in infancy. Compared with reactions obtained in later childhood, those in the infant are likely to be smaller, especially in the size of the wheal. The erythematous flare may be 2 cm. in diameter or larger. The difference is due mainly to the characteristics of the young child's skin. The limited number of foods which comprise the infant's diet makes the clinical evaluation comparatively simple. At this age we are concerned chiefly with possible sensitization to milk, egg and wheat. A few additional but less important foods such as orange, banana, carrot, pea, peanut butter and tuna fish, which are widely used during the first two years of life, may also have to be reckoned with.

This is what Hill[6] said in 1951 about the significance of skin tests in general: "They are useful tools which sometimes do and sometimes do not point the way to the cause of symptoms under consideration." In 29 eczematous infants under 3 months of age Hill found 19 who gave positive skin tests to 8 different foods. Egg white gave positive reactions in 16 infants. Some of the positive reactions were of clinical significance.

More recently, in their study of milk allergy among infants under age 2, Bachman and Dees[1] selected 109 allergic infants for special investigation. Among the 109 infants, 37 gave positive scratch tests to cow's milk, of whom 33 were clinically sensitive and only 9 were not. This is an incidence of 73 per cent correlation between skin tests and clinical sensitivity.

In the case of suspected milk allergy in infancy a corroborative skin test may help, but is not essential. Observation based upon clinical results will suffice. Clein[3] actually reported such a study. He collected 140 infants under the age of 9 months, all of whom had clinical allergy to cow's milk. The diagnosis was based on clinical symptoms which were relieved when milk was withdrawn from the diet. The symptoms which these babies had as a result of milk sensitivity were mostly eczema, pylorospasm, severe colic, diarrhea, croup and choking. They were "transformed" into happy babies when cow's milk was replaced by soybean milk. In this study Clein completely ignored the skin tests.

I recently selected for review the case histories of 26 infants and children who were first seen under the age of 2 years, of whom 25 had atopic eczema, asthma or both, and 1 had chronic urticaria. They were selected consecutively from a larger series of children referred with a diagnosis of an allergic disease. This group, though small, may be considered to be a representative sample of allergic infants under age two, usually seen in the practice of a pediatric allergist, or in a pediatric

allergy clinic. Sixteen of the 26 infants were clinically sensitive to food. Most of them were sensitive to more than 1 food, so that the total number of foods they were sensitive to was 49. The 49 allergenic foods gave 36 positive and 13 negative skin reactions (Table 11). Those who were sensitive to egg white, nut and peanut, and the 1 sensitive to wheat, gave 3+ reactions or larger. Ten of the infants were not clinically sensitive to any food, but gave 44 "false positive" skin reactions to 23 different foods. Most of these falsely positive reactions were of the 1+ variety, however, with only a sprinkling of 2+ and 3+ (Table 12).

It should be noted that many of the foods that gave "false positive" reactions had never been eaten, or had been eaten once or twice, and for various reasons were rejected by the child. Therefore the extent of their clinical significance has yet to be determined.

From the foregoing it is evident that food sensitization is encountered fairly often in the initial two years of life among those who are allergically ill. Furthermore, there appears to be a significant correlation between clinically proved food sensitivities and positive food tests, which in the 16 infants herein presented was about 74 per cent (36 of 49). In the entire group of 26 children under age 2 there were 80 positive skin reactions (36 plus 44), 36 of which had clinical significance, an incidence of about 45 per cent correlation between clinical sensitivity and positive skin tests.

In order of frequency, egg white, nuts, milk, peanut, chocolate and fish were the most important allergenic foods. All the children who were clinically sensitive to egg white, nuts, peanuts, fish and shellfish gave large positive skin tests to these foods.

The milk sensitivities encountered in this group of infants call for

TABLE 11. *Correlation of Proved Food Sensitivities with Results of Skin Tests in 16 Allergic Babies*

FOOD	SKIN TEST	
	Positive	Negative
Egg white	9	0
Nuts	5	0
Peanuts	4	0
Orange	3	1
Fish	2	0
Shellfish	2	0
Milk	1	4
Chocolate	1	4
Banana	2	0
Beef	2	0
Wheat	1	0
Pea	2	1
Tomato	2	1
Sweet potato	0	1
Squash	0	1
Total	36	13

TABLE 12. *Falsely Positive Food Tests in 10 Allergic Infants Who Were Clinically Not Sensitive*

FOOD	FALSE POSITIVES
Egg white	4
Egg yolk	2
Wheat	4
Rye	1
Oat	1
Milk	3
Chicken	3
Beef	2
Pork	1
Fish	2
Shellfish	1
Prune	2
Orange	2
Banana	1
Potato	2
Pea	2
Beet	1
Tomato	1
Carrot	2
Corn	1
Nut	3
Chocolate	2
Peanut	1
Total	44

special consideration. Of the five infants clinically sensitive to milk, only one gave a 2+ reaction to it, and four gave negative tests. However, there were three infants who gave positive milk reactions which were of no importance. It is likely that milk sensitization is present mostly in the first few months of life. It may be lost before the first birthday, but in a few the test remains positive for a long time.

Only 1 baby had clinical sensitivity to wheat (4 per cent). Its skin test was positive, but four others gave positive wheat tests that had no significance at the time of this study. A glance at Table 11 quickly reveals that almost any food could be allergenic in this age group.

The Positive Egg White Test

The positive egg white test in infancy is of special interest. It occurs often in atopic eczema, and also in a good many babies with asthma. Sometimes these infants have frightful symptoms when egg white is eaten, but the symptoms are usually angio-edema or urticaria, and not eczema or asthma, which are their chief complaints. Hill[7] believes and almost proves that an unknown immunologic factor which he calls the "X-factor" is present in the skin of the eczematous infant. A combination of the unknown X-factor and the urticarial type of sensitivity en-

gendered by a food such as egg white is necessary to produce the lesion of atopic eczema. If food sensitivity exists alone and without the X-factor, only transient urticaria will develop, and never eczema.

As stated above, a good many eczematous infants produce positive skin tests to egg white. If clinical sensitivity to egg is also present, the infant who accidentally eats it will have pruritus or urticaria, and seldom eczema. Even when it appears that the eczema has been made worse by the egg, one cannot be certain that the two facts are related to each other. In fact, it is more likely that itching and urticaria, which are manifestations of food allergy, when superimposed upon the lesion of eczema, would naturally appear to make the eczema more intolerable.

Buffum,[2] who for many years has studied asthma in early infancy, believes that a large positive skin reaction to egg white in an asthmatic infant is a bad prognostic sign and that these infants are likely to have a rough time. If this observation is correct, and there is evidence that it is, the egg test may be used not only as a guide to possible clinical sensitivity to it, but also to prognosticate the probable course of asthma in a young child. In the presence of a large positive egg white reaction it is best to avoid it, but if the egg test is negative or feebly positive, one may feed it on a trial basis. Not infrequently a positive egg test is not associated with allergic symptoms (Table 12). This is not an unusual phenomenon. It is encountered with almost every allergenic substance. Pollens, molds, environmental inhalants and animal danders may exhibit the same phenomenon, though not as frequently as with foods.

In connection with egg white sensitivity we must keep in mind that in this day and age certain viral vaccines are prepared on culture media containing chick embryo nutrient. Such vaccines may be allergenic to egg-sensitive children and should therefore be administered with caution.

Clinical Significance of Food Reactions in Infants under Two Years of Age

The question frequently asked is: Should we do skin tests at all on small children? Also, of what clinical value are they? These questions have been pondered by many pediatricians and allergists for a long time. The answer to the first question is yes, because there is much one may learn by doing skin tests with foods. The second question is answered best by examining the possible benefits derived from food tests. It is believed that in the presence of large positive skin tests one may feel secure in the assumption that the child is an atopic one. Nonallergic children seldom, if ever, will give large positive skin reactions. In this instance the test has distinct diagnostic value. In severely ill allergic children, especially those who are already on a restricted diet because

of known or alleged food sensitivities, food tests may be used as a guide before introducing foods which had never been eaten. Most of the time parents tell the physician what foods the child could not eat. In the presence of large positive skin reactions, let us say to nut, peanut, egg or fish, the physician may caution the parents about these foods. The food in question may then be offered to the child in small amounts and under supervision until a correct evaluation has been established. Conversely, in the absence of a positive test to a food which is suspected by the parents, the physician will appear justified in advising a family to try the food under suspicion.

We frequently encounter positive skin tests to pollens which at the time of testing had no significance, only to discover one or two years later that the test has become clinically valid. Could this not also be the case in food allergy, especially in the very young? Thus a positive food test in a very young child may be indicative of possible future clinical sensitivity, and should be kept in mind as long as the infant continues to have allergic symptoms. Not infrequently we encounter a child with asthma, eczema or chronic urticaria who gives positive food tests, but no other significant etiologic clues. In this instance the positive food test may be of help as a guide for trial elimination diets.

In conclusion, there is evidence that in the young child there is considerable correlation between positive skin tests and clinical sensitivity to food. Therefore the test is believed to be a useful adjunct in the management of allergic disease in some instances. The manifestations of food allergy are usually urticaria and angio-edema. The eczema and asthma that plague these babies are not materially influenced by their food sensitivities. Seldom, if ever, do we solve the eczema or asthma completely by withdrawing the foods to which these infants are sensitive.

CLINICAL SIGNIFICANCE OF SKIN REACTIONS TO FOOD IN LATER CHILDHOOD

As the atopic child grows older the new contacts made, be they inhalants or foods, will accordingly complicate his allergic make-up. New foods, especially those commonly eaten, may result in additional sensitizations. Some of the foods which during infancy were important as a cause of symptoms may lose their clinical significance. The skin as an immunologic organ will participate in the child's immunologic processes by producing a stronger and greater yield of positive skin reactions, and these will now require greater scrutiny. In later childhood the food test may be large and frequently of much greater intensity than their counterpart seen during infancy. On the other hand, it will probably show less correlation with clinical symptoms, although this

will depend upon the food in question. A large number of positive food reactions will have no clinical significance at all. Just as in infancy, there will be the ever-disturbing food which is known to produce clinical symptoms, but will nevertheless produce no positive skin reactions.

The older child will eat a larger variety of foods. He will also eat foods which are potentially more allergenic, such as nuts, peanuts, fish and shellfish. Although he may now tolerate some of the foods which in earlier childhood produced clinical symptoms, the total number of potential food sensitivities will be larger.

About 50 per cent of the allergic children whose disease is perennial asthma or atopic eczema will give a positive history of food allergy. About 55 per cent of the children with these diseases will produce positive skin reactions. By contrast, seasonal asthma and hay fever appear to have an extremely low index of food sensitivity (less than 5 per cent), and an equally low incidence of positive food tests (a little over 5 per cent).

The correlation between clinical food sensitivity and skin tests will depend upon the food under consideration, the age and upon the disease the child has. Fish, shellfish, nuts and peanuts will show from 90 to 100 per cent correlation between clinical sensitivity and results of skin tests. Egg shows about 60 per cent correlation, and with other foods it will range from 0 per cent upward.

A few additional statistics are now in order. Hill[5] collected 100 asthmatic children of all ages and found that 35 gave positive skin reactions to foods. The 35 children gave 218 positive skin reactions, but only 44 had clinical significance, an incidence of about 20 per cent. This is a much lower incidence of correlation between clinical and skin test sensitivity than was encountered in infancy.

In 97 allergic children studied consecutively, all of whom had atopic eczema and nonseasonal asthma, Freedman and Sellars[4] found that 56 (57 per cent) gave positive skin tests to 1 or more foods, and 41 gave negative tests. Of the 97 children, 47 (49 per cent) were proved to have food sensitivities by clinical criteria. They were sensitive to 121 foods, 85 of which gave positive and 36 gave negative reactions, an incidence of 72 per cent correlation. The high incidence of proved food sensitivity and of positive food tests in the group could be due to the fact that these children had moderate to severe atopic eczema and nonseasonal asthma—the most serious allergic diseases. In 38 allergic children also studied consecutively, all of whom had hay fever and/or seasonal asthma, they found only 3 (about 8 per cent) who gave positive skin reactions to food, and 35 gave negative tests. This is only one seventh the frequency of positive food tests found in children with atopic eczema and perennial asthma.

Among 150 children of all ages, but under age 13, all of whom were seen consecutively with a diagnosis of an allergic disease, the same authors found that 75, or 50 per cent, gave no evidence of food sensitivity either clinically or by skin test. By contrast, of the 97 children referred to above whose diagnosis was either perennial asthma, eczema or both, only 30, or 31 per cent, produced no evidence of food sensitivity either by history or by skin test.

THE SKIN TEST

In spite of differences of opinion as to its merits, one looks upon the skin test as a beautiful phenomenon of allergy. True, its accuracy in the case of suspected food allergy is variable, but the fact remains that it is a constant finding in many, if not in most, allergic persons. (See also p. 663.)

The *scratch test* is probably the technique most frequently used. The anterior surface of the forearm or the back is the usual site for testing. This test is now almost 100 per cent safe. It is practical, most easily performed, and in most instances fulfills the requirements of a case under consideration.

The *intracutaneous technique* is also used extensively. This test should be performed only after a negative reaction has been obtained by the scratch test. The anterolateral surface of the upper arm is the most suitable site. It is also the safest site, and will permit application of a tourniquet in the event of a constitutional reaction. One should not do an intracutaneous test on the back. It is well to remember that fatalities have occurred from intracutaneous skin testing, and the risk is still present. This test is likely to give more falsely positive reactions than the scratch test. For this and other reasons Hill has abandoned the intracutaneous food test in favor of the scratch test in recent years.

Commercially prepared food extracts are most frequently used for skin testing. For the scratch test the food allergen is prepared in 50 per cent glycerin, which is believed to enhance its stability. For the intracutaneous test, aqueous food extracts are used by most physicians and clinics. Commercial food extracts are well made, are easy to procure and convenient to use. However, the active food allergen in a commercial preparation may not remain stable very long. Furthermore, the allergenic substance in a commercially prepared solution may have been altered in the process of extracting, so that it is no longer the same as the antigenic substance in native food.

NATURAL FOODS AS SKIN TESTING MATERIAL

In 1942 Tuft and Blumstein[9] published their observation on three adult patients who exhibited typical allergic symptoms upon eating fresh

fruits, but whose skin tests to stock extracts were negative. They then tested these patients with extracts and powdered testing materials from several other laboratories, and again were unable to obtain positive skin reactions. They then resorted to the use of freshly squeezed fruit juices, and were surprised when they obtained consistent positive skin tests. To rule out possible irritating properties of fresh fruit juices, they tested allergic patients who had never had food allergy, as well as nonallergic normal persons. In the two latter groups fresh fruit juices never produced a positive skin test.

It was also found that fresh fruit juices retain their antigenicity for only a few hours. After this period the antigenic properties begin to fade, disappearing completely in one to four days. Seitz filtration and heating also resulted in the loss of antigenicity. Rapid freezing as in frozen food, on the other hand, seemed to preserve the antigenic qualities of fresh fruit. These authors have, therefore, demonstrated that in the case of fresh fruit there was complete correlation between results of natural food tests and clinical sensitivity. This did not occur when stock extracts or powdered foods were used.

For several years I have used natural foods as skin testing material. It was found that natural foods may give larger reactions than commercially prepared extracts. Frequently natural food tests give positive reactions, whereas the corresponding commercial extracts give negative or weakly positive reactions. Only the foods commonly eaten during infancy and childhood are tested for. Egg white, yolk, milk, wheat, haddock, mackerel, walnut, peanut, chocolate, orange, banana, pea and potato are the foods used. Additional foods may be added to the list whenever indicated.

The parents are instructed to prepare these foods in advance. Each perishable food is wrapped in tinfoil and placed in the freezer. The foods are taken out just before coming to the office or clinic. Only a small piece of each food, the size of a penny, is needed for the test. The skin is scratched in the conventional manner. In our clinic we do three small light scratches. Egg is boiled two minutes. The white and the yolk are wrapped separately. Fish is tested in its raw and cooked states. The foods are cooked in water without seasoning for a few minutes. Cottage cheese and whey are used when testing for milk sensitivity. Baker's chocolate and whole wheat flour are the materials used. Peanuts and nuts are crushed on tinfoil and applied to the scratched skin. Generally, the food used for testing should be in the state in which it is commonly eaten. Dry foods such as chocolate or whole wheat are thoroughly moistened with buffered saline. Orange and tomato are used as they occur in their natural ripe form. All natural food tests are performed by the usual scratch technique.

Seventy three children with atopic eczema and/or perennial asthma,

TABLE 13. *Comparison of Results of Skin Tests with Natural Foods and with Commercial Extracts Performed on 73 Children with Atopic Eczema and/or Perennial Asthma*

DISEASE	NUMBER OF CHILDREN	COMMERCIAL EXTRACTS			NATURAL FOODS		
		Neg.	1+	2+ to 5+	Neg.	1+	2+ to 5+
Asthma	29	76	23	22	73	15	33
Atopic eczema	20	40	20	22	33	12	37
Asthma and eczema	24	102	37	25	70	20	74
Total	73	218	80	69	176	47	144

The age ranges were as follows: under 6 months, 5; 6 months to 2 years, 21; 2 to 5 years, 26; 5 to 12 years, 21.

all of whom had evidence of food allergy, were tested with natural foods and with commercial extracts. The results are shown in Table 13. Commercial food extracts gave more negative tests than the corresponding natural foods (218 to 176). About twice as many large positive reactions (2+ to 5+) were obtained with natural foods than with commercial extracts (144 to 67).

A comparison of results of skin tests with 16 natural foods and their corresponding commercial extracts on random children with atopic eczema and/or perennial asthma is shown in Table 14. Many more foods gave mildly positive (1+) reactions with commercial extracts

TABLE 14. *Comparison of Results of Skin Tests with 16 Natural Foods and Their Corresponding Commercial Extracts in Random Children with Atopic Eczema and/or Perennial Asthma*

FOOD	COMMERCIAL EXTRACTS			NATURAL FOODS		
	Neg.	1+	2+ to 5+	Neg.	1+	2+ to 5+
Milk	45	10	4	44	2	13
Wheat	32	17	2	27	5	21
Egg white	44	18	17	34	4	41
Egg yolk	17	5	4	14	1	11
Fish (mackerel, haddock)	17	7	12	13	2	21
Shellfish (shrimp, crab meat, lobster)	5	2	6	5	1	7
Walnut	23	6	8	12	14	11
Peanut	16	12	15	16	5	22
Chocolate	31	3	0	22	8	4
Tomato	15	4	3	11	9	2
Potato	4	2	5	1	3	7
Beet	0	5	0	3	0	2
Carrot	3	3	0	4	0	2
Pea	9	5	2	8	3	5
Lima bean	2	2	3	1	3	3
Orange	23	2	0	15	7	3
Total	283	103	83	230	67	175

than with natural foods. However, large positive reactions (2+ to 5+) were obtained more than twice as often with natural foods as with commercial extracts (175 to 83). It is safe to assume that the large positive reactions were much more likely to have clinical significance than the small 1+ reactions. These figures seem to indicate the probable superiority of natural foods over the commercial extracts as skin testing materials.

Figure 24 shows five natural food tests done simultaneously with corresponding commercial extracts. Figure 25 shows the results of the tests. Natural egg white, raw potato and peanut produced larger reactions than the commercial extracts, but egg yolk was positive with commercial extract and negative with the natural food. Both cottage cheese tests were negative.

When using a natural food as testing material, one should take the same precautions as are taken for the intracutaneous test. The arm, not the back, should be the testing site. I witnessed a constitutional reaction from a raw potato scratch test, and also a near-fatality from a brazil nut test. Dr. William Sellars from Dallas, Texas, recently witnessed a frightful constitutional reaction in a small child when a scratch test was done with natural raw egg white (personal communication).

Fig. 24. Natural food tests. *Right*, Natural foods; *left*, commercial extracts. All tests were performed simultaneously.

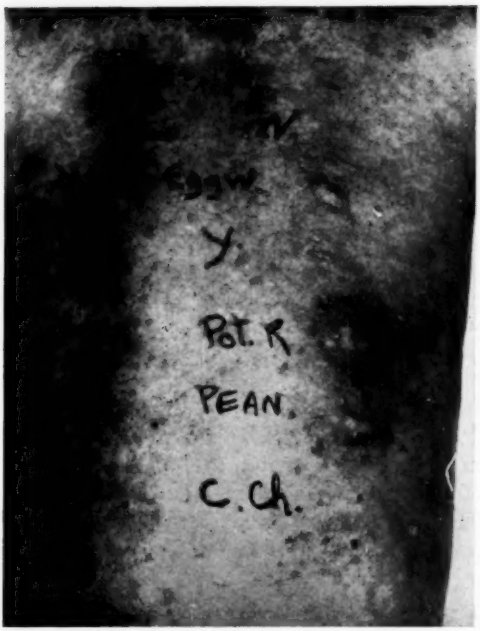

Fig. 25. Results of tests. *Right*, Egg white, raw potato and peanut show larger reactions than the commercial extracts on the left. *Left*, The egg yolk reaction with commercial extract is positive, but the natural yolk reaction is negative. Both cottage cheese tests were negative.

SUMMARY

Allergic infants as well as older children frequently give positive skin tests to foods. In those with atopic eczema and nonseasonal asthma the incidence of positive food tests may be seven times greater than in those having hay fever or seasonal asthma. The incidence of positive skin tests to foods in the general allergic childhood population is about 50 per cent.

Clinical sensitivity to food is probably most prevalent in young eczematous and nonseasonal asthmatic children. In the 97 such children presented above the incidence was 49 per cent.

There is significant correlation between positive skin tests and clinical sensitivity. The extent of this correlation is probably much greater in very young children, and may diminish as the child grows up. This diminishing correlation may be explained, in part at least, by the fact that frequently foods which were known to produce allergic symptoms in earlier childhood are tolerated a few months or a few years later, but the positive skin test remains. It is important that "false positive"

skin reactions be recognized so that no clinical significance will be attached to them.

The degree of correlation will also depend upon the food in question, being almost 100 per cent in nut, peanut, fish and shellfish sensitivity, and about 60 per cent in egg sensitivity. Other foods have a much lower degree of correlation.

The manifestations of food allergy are mostly urticaria, angio-edema, gastrointestinal upsets, herpetic lesions about the mouth, and occasionally shock. The course of asthma and eczema is usually not affected by the existing food allergy. Even when the asthma or eczema appears to be made worse by a food, it is usually of minor importance. This is especially true after the second year of life.

Natural foods make good testing material and are probably more reliable as an index of clinical allergy than the commercially prepared extracts. They give larger reactions, and at times they give positive tests where commercially prepared extracts give negative tests. Natural food tests should be given further trials. They should be used cautiously, especially if the child to be tested is known to have food allergy.

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FACTORS INFLUENCING CLINICAL EVALUATION OF FOOD ALLERGY

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The reader in allergy can be excused if he suffers from confusion among the conflicting opinions expressed on the role of foods in the causation of allergic disease. A critique of all these opinions can hardly be attempted in a brief discussion of this sort. I have, therefore, merely tried to give a practical orientation to the untoward effects of food as they appear as problems in daily medical practice.

It is common to regard food allergy as synonymous with gastrointestinal allergy. Although it is true that the gastrointestinal tract is the most commonly affected shock organ, any tissue of the body may participate in the allergic reaction. Food allergy is an exaggeration of the immune response to food, mediated by an antigen-antibody relationship with no regard to the site of the reaction. Perhaps it might be more specific to speak of allergy to ingesta rather than of allergy to food, since drugs and inhalational substances which reach the gastrointestinal tract produce reactions in the same way that food does.

THE ALLERGIC RESPONSE

Symptoms

Since any tissue of the body can be provoked to an allergic response by specific foods, the possible symptoms are too numerous for coverage other than in a textbook. Obviously, reactions from foods in the respiratory passages result in asthmatic and rhinitic symptoms; in the skin, in dermatitic lesions; and in the gastrointestinal tract, in disturbed physiologic function. Acute, generalized systemic reactions occur, too, although rarely.

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Reactions occur predominantly in the gastrointestinal tract, since this is the organ most naturally, most directly and most frequently exposed to the antigen. Experiments on the exposed digestive tract of passively sensitized human beings and rhesus monkeys determined that clinical reactions consisted in mucosal edema, hyperemia, and hyperactivity of the secretory and mucosal glands of the intestines, with secondary muscle spasm.[47]

Clinical symptoms, depending on the portion of the tract involved, include swelling of the lips and buccal mucosa, vomiting, abdominal pain, diarrhea, pylorospasm,[20] pruritus ani, and other miscellaneous reactions such as mucous colitis[28] and rectal bleeding.[40] These gastrointestinal disturbances have been carefully studied by radiologic techniques[24, 25] which have revealed delayed emptying, hypotonicity of the stomach, and hypertonicity of the small intestine. Such findings in themselves are not diagnostic of allergy, but are contributory evidence.

Allergic abdominal pain has been classified by the author,[23] depending on severity, as follows:

1. Severe abdominal pain, simulating an acute surgical condition of the abdomen in which differentiation from appendicitis, gallbladder disease, and so forth, is challenging.
2. Abdominal pain of subacute recurrent nature.
3. Abdominal pain as a subsidiary symptom (appearing during acute attacks of asthma or, more often, during severe outbreaks of urticaria or angioneurotic edema, or as part of a constitutional reaction.

Although there has been some question as to the role of foods in the etiology of atopic eczematous dermatitis,[10] my experience would encourage me in the belief that in some instances foods play a definite role, egg perhaps being the most frequent causative agent.

The provocation of urticaria and angioneurotic edema by shellfish and seafood is a common experience, and points to the likelihood that other foods are potentially urticariogenic.

Rhinitis and bronchopulmonary reactions occasionally follow ingestion of foods. More commonly the respiratory reactions to foods are due to inhalation; viz., "baker's asthma" due to inhalation of wheat, and the asthma induced in those occupationally exposed to castor bean dust,[17] which is an extremely active allergen.

Such symptoms as "restlessness," "diaper dermatitis,"[35] "frequent upper respiratory tract infection," and the like, are not of established allergic etiology and are too loosely named to qualify as food allergies.

There are syndromes composed of symptoms occurring in disparate parts of the body which are becoming recognized as being provoked on occasion by an allergic reaction to foods. Exemplifying these are Henoch-Schoenlein purpura,[1] celiac syndrome,[15, 32] recurrent vomiting,[12] pylorospasm,[20] and ulcerative colitis.[40]

Several American authors have hypothesized that food allergy is a factor in celiac disease, milk predominantly, but other foods have

also been incriminated.[32] In a series of contributions by Dutch writers[13, 50] wheat, rye and oats are inculpated. However, their evidence for an immunologic mechanism is not convincing. On the basis of the material presented a nonallergic etiology would be more probable. Subsequent reports from other parts of the world on identification of celiac symptoms with adverse reactions to wheat and oats discount an allergic etiology, primarily on the basis of negative cutaneous tests obtained.[2, 9, 15] In contrast is a single case reported in which steatorrhea was associated with the ingestion of small amounts of beta-lactoglobulin of cow's milk, with correlating positive intracutaneous tests.[11]

Some of the symptoms of allergy to foods are teleologically protective reactions. Such common disturbances as vomiting and diarrhea are propulsive methods of ejecting rapidly the noxious foods. In acute anaphylactic reactions due to exquisite sensitiveness to foods, the vomiting which usually terminates the episode is undoubtedly a protective mechanism. I have in mind a particular instance of milk sensitivity in an asthmatic child in whom the reaction to a small quantity of milk was of such severity it could have been terminated only by either the vomiting which occurred, or by death. Nausea or abdominal pain sets off a conditioning process. After several experiences the ingestor will often subconsciously refuse these foods. Even in the infant unpleasant consequences of food ingestion, after one or two trials, teach him to reject this food.

Parenteral Absorption

Absorption into the gastrointestinal tract of inhaled substances has been reported. Although the original studies were done with copper dust,[46] one might assume that pollen, particularly during the heavy inundation of the pollen season, enters the digestive tract in the same manner and acts as antigenic food substances. Attempts at oral hyposensitization with pollens have been complicated by gastric disturbances produced by the pollens so introduced.[42]

Inhalation of fine particulate food substances directly through the respiratory mucous membrane into the blood resembles the absorption of aerosolized drugs via nebulization, and involves another route of introduction into the body of antigenic material. Such antigenic particles have been termed "osmyls."[46]

The permeability of the intact integument to food contactants is small. Nevertheless, in highly sensitive subjects, despite the minor amounts absorbed percutaneously, foods are capable of producing localized urticarial rashes at the site of contact, or even widespread systemic reactions. A seven-year-old child with asthma, and positive cutaneous test and clinical reactivity to ingestion of peanut, demon-

strated on several occasions that peeling a peanut from its shell produced local and disseminated urticaria. Swelling of the lips and of the linings of the mouth on labial or buccal contact with egg or fish in specifically sensitive children is well known.

The extremes to which such reactivity can go are illustrated by an instance known to me of a patient who reported to his physician localized urticaria on cutaneous contact with Brazil nut. In an attempt to verify this seemingly bizarre story, the physician rubbed vigorously on the skin of the subject's forearm the cut surface of a Brazil nut, producing immediate, fatal anaphylaxis.

This specific allergic reaction is in contrast to the cheilitis, or contact eczematous dermatitis of the lips, or circumoral erythema seen after exposure to certain vegetables and fruits. Such reactivity represents an idiosyncracy in those persons whose threshold is below the average to the nonantigenic irritants contained in orange, spinach, celery, and the like. These foods contain essential oils which act as primary irritants and are well documented as industrial hazards to those handling them in farming and food processing.[27] Celery contains, among other ethereal oils, limonene, which is common to orange and has an eczematogenic factor. Negative scratch and intradermal tests are obtained in persons giving this type of contact reaction.

FOOD AS AN ALLERGEN

Theoretically, almost all foods are capable of provoking an allergic reaction. Obviously, those which are most potent antigenically, or are most frequently eaten, are the most frequent offenders. Egg, milk, fish, legumes and wheat are therefore the foods commonly implicated.

Classically, atopic clinical reactions resulting from ingestion of a food, such as asthma, allergic rhinitis, urticaria, angioneurotic edema and anaphylactic shock, are in themselves indicative of an immunologic mechanism. In the lack of such classic allergic manifestations, diagnosis is dependent on corroborative evidence.[19]

Confirmatory positive cutaneous tests, a personal history of allergy, or, of less value, a history of allergy among the immediate collaterals can be valuable aids to diagnosis. In appropriate circumstances of alimentary involvement, properly controlled roentgenograms of the gastrointestinal tract can be revealing. Eosinophilia in the mucus of nasal or bronchial secretions or of the blood can sometimes offer the necessary confirmation.

There are several immunologic mechanisms which motivate the allergic response, all coming under the general definition of antigen-antibody reactions. In the human being most commonly the reagin, or skin-sensitizing antibody, initiates the allergic reaction.[10] Other allergic reactions involve a precipitin mechanism,[14] a complement-fixing mechanism[4] or a leukocytotoxic mechanism.[5]

It is the reaginic mechanism which usually yields a positive cutaneous test to the offending food, by direct or passive transfer methods.[10] This procedure of testing has limitations in diagnosing food allergy, since it is not regularly obtained.

Coca,[8] whose contributions to allergy have always merited serious consideration, has theorized that nonreaginic allergy to foods is an inherited sensitivity whose presence can be determined by an acceleration of the pulse rate after food has been ingested. His inclusion of such bizarre reactions to foods, as determined by this test, as petit mal, pyrosis and coronary disease is most unexpected. This theory I find difficult to accept.

Cutaneous Tests

Cutaneous tests to foods do not correlate so well with symptoms as do cutaneous tests to inhalants. Nevertheless, they occur with sufficient frequency as to make their use worth while. They correlate best where they are least useful—in those patients with immediate demonstrable reactions following ingestion.[18]

Apparently there is sometimes a smaller concentration of reagins in the skin than in the reacting tissue. Positive cutaneous reactions in clinically sensitive subjects are sometimes obtainable with extracts of higher potency, with controls negating any nonspecific irritant effects.[18]

It is also possible that sensitivity may exist specifically to the digested product of foods—to the proteose or other split derivatives of protein—and not to the unaltered foods.[43]

Furthermore, the absence of reactions in some subjects may be due to the operation of immunologic mechanisms not mediated by a skin-sensitizing reagin.

Duration of Food Sensitiveness

It is not unusual for persons sensitive to a food to remain reactive for life. On the other hand, as a general rule, there is a tendency for food sensitiveness to wane gradually if re-exposures are avoided, although in some instances this spontaneous waning takes place despite exposure. Although attempts at active hyposensitization have not been rewarding, prolonged avoidance in most persons and with most foods would seem to produce tolerance. Chief exceptions to this would be fish and nuts, sensitivity to which is rarely lost. Understanding of the mechanism which determines this behavior is still lacking.

I have seen reactivity to foods last as short a time as three to four weeks, and have also observed the persistence of symptoms to foods for many years with the assumption that they would last for life.

In some studies which I am accumulating to report on egg hypersensitiveness, only those cases were chosen in which there was correlation of clinical symptoms with cutaneous and conjunctival sensitiveness. With the passing of time the loss of clinical sensitivity roughly paralleled the loss of cutaneous sensitivity. In some instances, however, loss of objective reactivity preceded—or followed—loss as indicated by testing. These results were obtained only by studying the patient over a period of several years. At any one time one may get clinical sensitivity with negative cutaneous tests, or loss of clinical sensitivity with cutaneous tests still positive as evidence of previous susceptibility.

Frequency

Therefore the incidence of food allergy is not fixed. It decreases progressively with maturity. Under ideal circumstances of accurate diagnosis the incidence, if plotted, would be a falling one with increase in age.

Moreover, food allergy does not lend itself to a statistical evaluation: diagnosis is often faulty, since rigid clinical criteria are rarely applied in medical practice.

Reported incidence in the literature shows a variation from 0.3 to 55 per cent,[19, 37] depending on the sampling and on the latitude of diagnostic criteria used. With the increasing enthusiasm for diagnosis of food allergy, the incidence will become even higher, to judge from the tendency to ascribe unexplained symptoms to food ingestion.

Allergenicity of Food Contaminants

The inadvertent introduction into foods for human consumption of antibiotics and penicillin via their administration to poultry and cattle is a matter of concern. Noteworthy are the surveys of the Food and Drug Administration[48] on random samples of milk. In 11 per cent penicillin in concentrations up to 0.55 unit per milliliter was found. There were also trace amounts of other antibiotics such as the tetracyclines and bacitracin. Gastrointestinal and even systemic allergic reactions from these are probable in highly sensitive persons. The possibility of the sensitizing of human beings by repeated ingestion of trace amounts of penicillin may account for some of the inexplicable reactions occurring after the first injection of this drug. Legislative controls advocating that milk from penicillin-treated cows not be sold until 72 hours after the last injection are now being tried.

An appeal to appetite is frequently achieved by the addition of coloring matter to foods. Although these contaminants are tested for their possible toxicity, little thought is given to their potential allergenicity.

These dyes can be divided into three major groups: coal-tar dyes, natural dyes derived from plants and animals, and inorganic or synthetic pigments. Although little investigation has been done in this field, it would seem that the coal-tar dyes are potentially the most allergenic.

One must also consider the possible allergenic role of otherwise safe preservatives and even of pesticides[7] used on growing plants and in animal feed, transmission of which to the human ingestor is subject to inspection.

NONIMMUNOLOGIC INTOLERANCE TO FOOD

In the observation of reactions caused by foods, distinction must be made between those mediated on an immunologic basis and those provoked by nonimmunologic incitants intrinsic in foods or by nonatopic susceptibility of the ingestor. Identical symptoms may occur from food allergy or from nonimmunologic intolerance.[19] Identification of the mechanism should be made in order to provide more intelligent management of the patient, and also for the sake of scientific accuracy.

The disappearance of symptoms with the removal of a suspect food from the diet and reappearance with refeeding has been gaining favor as a diagnostic indication of food allergy. It cannot be repeated too often that this method simply incriminates the incitant, but does not specify the mechanism by which the disturbance is induced.

Ingenerate in the Food

Earlier in this paper mention was made of several nonantigenic reactions induced by foods. Following are other examples of nonimmunologic intolerance which deserve consideration. In foods in which Staphylococcus is propagated, toxins are formed in large quantity.[30] An immediate gastroenteritis usually is induced by ingestion of foods which have been thus contaminated. The diagnosis of food allergy is often made, especially when the circumstances and the clinical picture are not carefully evaluated.

Furthermore, some rare ingesta are causative of profound gastrointestinal or systemic effects because of the presence of inherent toxins. Certain types of mushrooms, shellfish or poisonous fish are examples.

Many foods have, intrinsic in their chemical structure, pharmacologic effects which operate in varying degree on many persons. An obvious example of this is the laxative effect of prunes, probably due to the diphenylisitin naturally contained.[19] Soybean, particularly when ingested in large quantities as in the use of soybean milks, acts as a gastric irritant producing abdominal distress, diarrhea and sore buttocks, and occasionally vomiting in predisposed persons. This pharmacologic

effect is probably due to the bulk of the cellulose content of the soybean, or its alteration of the pH of the stools, or to the trace amounts of soyin,[33] and not to its operation as an antigen.

Ingenerate in the Host

In some instances unusual biochemical disturbances of metabolism, perhaps as a consequence of hereditary defect of the enzyme system, impair proper synthesis of foods. As a result, there is an accumulation within the organs of the body of substances capable of serious disturbance. Such disturbances would include the metabolic disease of galactosemia.

Galactosemia (see also p. 885) is a familial disorder characterized by an intolerance of galactose. Milk sugar (i.e., lactose), a disaccharide composed of glucose and galactose, is improperly metabolized, resulting in storage of galactose in the organs of the body. The abnormal quantity stored may lead to hepatosplenomegaly. The intracellular accumulation of galactose, especially in the liver, kidney, lens of the eye and brain, has serious implications for the development of cataracts and of mental retardation. The symptoms vary in intensity, paralleling the severity of the disease. Vomiting, diarrhea, anorexia and swelling of the abdomen are all directly attributable to the ingestion of milk.[12]

Strict elimination of milk and milk products from the diet, even in trace amounts—far beyond the precautionary avoidance desirable in allergy to milk—is essential to recovery. Obviously, no immunologic mechanism is involved in this disease process, yet removal of the offending food results in control of symptoms.

Other food-induced diseases, easily parading as allergic ailments, are breast milk intoxication,[16] goat's milk anemia[36] and favism.[34] In the first, vitamin B deficiency in the mother produces toxic substances in her milk capable of provoking severe systemic illness in the child. A macrocytic type of anemia has been reported following prolonged feeding with goat's milk, attributable to its low content of vitamin B_{12}

Favism has been described as an allergic disease, based on sensitivity to fava bean, sometimes with correlating cutaneous tests. It is more probable that this disease, like galactosemia, or like the hemolytic anemia due to sensitivity to primaquine,[6, 44] is motivated on a non-immunologic—possibly hereditary and gene-controlled—basis.

It is my impression that hereditary defects in the cells which impair important enzyme reactions may account for instances of familial intolerance to a food. This I have observed in reference to egg, wherein some three generations were intolerant, in whom no positive cutaneous tests could be obtained, nor any evidence of associated allergic manifestations, nor history of familial allergy. The symptoms of this egg

intolerance were essentially gastrointestinal. These inherited disturbances may follow a mendelian transmission, the nonreactors behaving as transmitters of the disease.

PSYCHOLOGIC CONSIDERATIONS

No modern discussion of allergy is complete without some consideration of psychologic factors. Nevertheless it is difficult to accept the impression of some authors that all reactions to foods are motivated primarily by the psyche. The evocation of positive cutaneous tests in a patient who also gives, as controls, negative tests to other foods, and who is clinically reactive, should argue against such all-inclusive theorizing.

The attempts reported of feeding suspect foods concealed in capsules may eliminate the psychic element, but the quantity which can be so introduced is too small to incite symptoms in any but the most exquisitely sensitive person.[39] It can hardly be depended upon as a diagnostic test, nor does it prove the psychologic attitude of the patient toward the food.

On the other hand, roentgen studies in which amounts known to cause gastrointestinal disturbances in highly reactive persons were introduced into the barium meal without the knowledge of the patient proved the reactivity of the ingestor despite elimination of psychic factors.[24, 25]

A reaction of distaste, nausea or vomiting to a food can sometimes be a conditioned reflex resulting from a previous adverse exposure to the food. Ingestion of spoiled food and consequent severe gastric distress, or overeating of a favorite food, can both create a psychologic block against future ingestion. This familiar mechanism again points out that gastric intolerance is not always of allergic etiology.

Also, the parent who forces excessive quantities of foods may induce extreme distaste and, possibly, may induce a specific sensitivity by overexposure to a potently allergenic food.

The awareness necessitated by special diets eliminating certain foods creates a varying degree of hypochondria in the patient, particularly those of teen-age.

An otherwise well behaved child will pilfer chocolate and/or conceal his chocolate indulgences. In many families the nutritionally important milk is never drunk without the addition of chocolate flavoring. With elimination of the latter, milk ingestion ceases. Although chocolate is a relatively unimportant food nutritionally, its ingestion is so much a part of our culture as to make its deprivation a matter of psychologic concern. A child who is forced to refuse chocolate does not seem to belong, and feels himself different from his playmates.

In view of the social import of this food, it is surprising that little has been done to produce a hypoallergenic chocolate.

DISCUSSION

Too little attention is paid in the presence of a substantiated allergy to foods to the botanically or biologically related foods to which sensitivity exists.[26] Falsely negative tests can be obtained to collateral foods which are more provocative clinically than the foods producing the convincingly positive tests. In analyzing the cutaneous tests of a patient in whom strongly positive reactions are obtained, consideration should be given to the importance of those of lesser reaginic content, or even of dubious positivity. Careful observation of the possible clinical reactivity of the patient to the related foods, regardless of the cutaneous tests, is essential for intelligent management.

Cross sensitization among members of food groups is frequent. Best known is that of egg to poultry, milk to beef, and between species of fish. Such biologic grouping is common in nature, as demonstrated by the relationship among some pollens. Sensitivity to legumes (the group including peas, beans, lentils, peanuts and soybean) is being encountered in early infancy with increasing frequency. It is likely that the widespread use of soybean in foods accounts for some of this increase. Particularly as a substitute for mammalian milk, soybean is introduced into the diets of many infants at an early age. Although sensitivity to soybean is reputedly rare according to the literature,[38] it does exist, and cross sensitization occurs to other legumes. In patients who had never ingested peas or beans, and who were clinically and dermally reactive to soybean, it was possible to demonstrate cutaneous tests to the other legumes. This cross sensitivity would seem to occur more frequently than that of milk to beef.[19]

As with every other ailment, allergy is subject to food fads. Zealous ingestion of wheat germ for its vitamin B effect, carrot for its vitamin A effect, citrus fruits for their vitamin C effect, may cause active sensitization to these foods, in view of the large amounts eaten over prolonged periods of time. One also sees the opposite: namely, the avoidance of milk for its alleged prophylaxis of allergy in infancy, and of citrus fruits and other mainstays of the diet for hoped-for control of indeterminate symptoms. These promiscuous avoidances lead in some instances to nutritional deficiencies and, at the very least, to a distortion of normality in the dietary habits of the growing child.

Nevertheless, ideal therapy would imply strict elimination of the offending foods or adulterants, should determination of these be possible. When the offender is an important, essential food, consideration should be given to the use of available deallergenized variants (i.e.,

evaporated milk instead of fresh milk, precooked or spray-dried cereals, dehydrated banana). The processing of these foods coincidentally alters the allergenic factor.[21]

In the lack of clear-cut assurance as to the causative agent, empirically determined hypoallergenic diets, eliminating the most frequent offenders, with adequate vitamin supplementation, are often satisfactory. When symptoms have been controlled for a time by such dietary management, the eliminated foods can be added one by one to determine any untoward effects.

Oral hyposensitization has not impressed me as a successful means of therapy.[31] It would appear that the successful results sometimes claimed are actually due to a waning of sensitivity which occurs spontaneously during the prolonged process of feeding gradual increments of the food.

Since sensitivity to foods is based on the potency of the food, the frequency of ingestion, and the constitutional reactivity of the ingestor, and since sensitivity occurs more frequently in children than in adults, it would seem logical that avoidance in early infancy of the more potent antigenic foods, such as egg, fish and legumes, might be worth while.

In depriving the diet—particularly that of the child—of essential foods, the physician assumes responsibility for compensating with adequate nutritional substitutes and vitamin supplementation. Not uncommonly, children maintained on such diets for prolonged periods of time evidence vitamin and other nutritional deficiencies as shown by stunting of growth, impairment of musculature and, in extreme instances of vitamin A deficiency, blindness.[3, 49]

In the future, nutritional deprivation of many essential foods will not be necessary. With the development of newer physicochemical methods for the separation of protein fractions and with the refinement of immunologic testing techniques, it will be possible to determine the specific fraction of a food to which sensitvity exists. Many of these fractions are amenable to alteration and hypoallergenization by heating, spray drying, enzymatic despecification and, in the future, possibly irradiating or sonic processing. With such selective denaturization, foods thus modified to eliminate the offending allergenic protein may still be available to the patient. We have seen the simple beginnings of such advances in the modification of milk by boiling or evaporating, which destroys the allergenicity of the lactalbumin fraction.

From the three major fractions originally identified in milk, some eight purer proteins have been subdivided.[29] Egg yolk has been demonstrated by chemical methods to contain some 6 fractions, and the egg white 10 distinct fractions, 1 or 2 of which are also found in yolk.[45] The use of techniques responsible for their isolation may some day make worth while the commercial preparation of a wide variety of foods in which the allergenic fractions have been rendered innocuous.[21]

CONCLUSIONS

The frequency with which the diagnosis of allergy is made in relation to foods makes it important to study more critically those investigative methods which are yielding substantial data today. Many diagnoses of food allergy which are currently made can be ascribed to a variety of pharmacodynamic effects, to misjudgment, to coincidence, or to wishful thinking in terms of current fads. Many of the incriminated foods, despite their evaluation as being causative, on further repetition do not survive the test of controlled retrial.

The future control of allergy to foods lies in a dual approach: first, more accurate diagnostic criteria, including differentiation from symptoms induced by nonimmunologic mechanisms; second, more informed approach to the diet of the allergic patient, which would utilize available hypoallergenized foods in an effort to maintain more normal eating habits and nutritional adequacy.

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ALLERGY TO COW'S MILK

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The history of cow's milk allergy follows and parallels the development of successful artificial feeding of infants with cow's milk formulas. In the period when no adequate substitute for human breast milk was generally available and before preservation, sterilization, sanitary economical processing of cow's milk were widespread practices only an occasional baby survived if he was deprived of his natural food. One of the great achievements of nineteenth and early twentieth century Pediatrics was the application and dissemination of newly discovered nutritional and bacteriologic principles to infant feeding. At the same time scientific advances in immunology were being applied to one after another of the human diseases. In the light of these discoveries it became apparent that an immunologic reaction might be a common basis for a group of heretofore seemingly unrelated disorders, so closely did they resemble immunologic reactions in experimental animals. The union of these three lines of investigation, namely, the perfection of substitutes for human milk, the mass production of these safe supplies of cow's milk, and the recognition of allergic reactions in human beings, has resulted in the emergence of a new clinical entity, cow's milk allergy, a twentieth century disorder.

Undoubtedly there have always been rare persons who were intolerant of or allergic to cow's milk, but their peculiarities have not been recorded. Not until the use of cow's milk became popular in recent years did sufficient numbers of people consume enough of it to afford the opportunity for the contact necessary to produce an allergy to this food in any recognizable number of persons. This is a situation comparable to the recognition of allergy to newly introduced drugs, with which there is usually a lag of some months or years before cases of hypersensitivity are detected and reported.

In the days when most infants were breast fed there were so few receiving any kind of substitute, and such a variety of hazards awaiting

the few not suckling mother or wet nurse, that in those who survived artificial feeding any problems which now might be attributed to an allergy were considered the expected result of an unnatural diet.[25]

In contrast to this, our current practice of infant feedings relies heavily on cow's milk as the initial and primary source of food. This is illustrated by the percentage of breast- and formula-fed infants reported by Meyer[31] recently in a survey of feeding practices in 1904 hospitals involving 2,225,000 infants. During 1956 these hospitals reported 21 per cent breast fed, 16 per cent breast and bottle, and 63 per cent bottle fed. This represents a nearly twofold increase in bottle feeding in the past 10 years, as indicated by a survey conducted under the auspices of the American Academy of Pediatrics, the United States Public Health Service, and the United States Children's Bureau in 1946 and 1947, in which they report finding 38 per cent breast-fed, 27 per cent breast- and bottle-fed and 35 per cent bottle-fed infants.

One can gain some idea of the enormous amount of cow's milk consumed in the United States by referring to the figures of the milk industry.[32] They state that United States consumers spent 6.9 billions of dollars for fluid milk products in 1957, during which year there was a per capita consumption of fluid milk of 305 pounds. In contrast to this, in 1910, per capita consumption of fluid milk was 252 pounds. During that same year, 1910, per capita use of evaporated whole milk was 1.5 pounds, while in 1957 it was 13.2 pounds. It is not surprising, in the light of these facts, that an occasional person will be found who is sensitive to a food which forms such a common item of the present American diet.

HISTORICAL

It is difficult to determine with certainty to whom credit should be given for the first description of cow's milk sensitivity. However, it would seem that Hamburger[21] in 1901 first clearly described an acute reaction to the feeding of cow's milk in an infant which resembled animal anaphylaxis. After this, Schlossmann and Moro[51] described the recognition of the specificity of lactalbumin in cow's and human milks by precipitin tests. In 1905 Schlossmann[49] reported on the toxic effects of foreign protein in the milk on nurslings. He describes 3 instances of acute reactions to the feeding of small amounts of cow's milk in infants of 2 to 6 months of age. These children all exhibited a syndrome of severe, acute prostration with vomiting, diarrhea, tachycardia, cold sweat, restlessness and collapse within a few minutes after feeding of cow's milk. Schlossmann postulated an antigen-antibody reaction as the cause of this prostrating illness. He also assumed that the protein passed unaltered through the gastrointestinal mucosa.

After this there appear in the literature reports of similar patients, among them one by Finkelstein,[13] who described five infants with this type of prostrating reaction. In 2 of his patients tolerance was accomplished by adding cow's milk, drop by drop, to the diet, in increasing amounts at daily intervals. He also reports on 1 infant who died with more severe symptoms after the third attempt at feeding of cow's milk. The child was given 10 gm. of a 1:3 dilution of milk, and immediately went into coma and convulsions. Autopsy showed serosal hemorrhage in the bowel, swelling of the renal cortex,

and slight edema of the lungs and brain. Two children, slightly older, had vomiting and severe diarrhea immediately after cow's milk feeding, but recovered. Finkelstein differed from Schlossmann in his opinion of the cause of this reaction to milk, feeling that it was due, not to a protein effect, but to some bacterial products in the gastrointestinal tract, although he clearly pointed out that this was a different problem from "cholera infantum."

Salga[48] in 1906 described 4 children who were fed with cow's milk and were skin-tested to determine whether this protected them against an injection of beef serum. In 3 of the 4 infants the injection of beef serum was followed by such immediate severe prostration and collapse that further studies were not possible on the patients. The fourth child received a succession of 4 injections of beef serum with reactions which diminished successively after the first injection, from prostration and diarrhea to no symptoms whatsoever after the tenth day of treatment. It was his impression that the feeding of milk did not give any immunity to beef serum, and that these proteins were immunologically distinct.

Reiss[44] reports on an infant of 3 weeks who had a similar severe reaction after ingestion of 100 gm. of buttermilk. He repeated a trial 1 week later with 60 gm. of 2:1 dilution of milk gruel, and within a quarter-hour the infant vomited 3 times, became cyanotic with sunken eyes, clammy skin, rapid pulse, dyspnea and labored breathing, and appeared to be dying. The baby recovered, and within 24 hours appeared relatively normal. Sixteen days after the acute episode 40 gm. of a 2:1 dilution of milk were tolerated without difficulty, and from then on the infant could be maintained on cow's milk formula. It was Reiss's impression that this severe reaction was due neither to foreign protein nor to foreign bacterial products, but was simply a response to an abnormal type of nourishment.

Schlossmann[50] in 1906 reported on an 8-week-old child who was known to be sensitive to cow's milk, having experienced a severe anaphylactic reaction after its ingestion, and who was treated with a series of calf serum injections and thereafter had no further reaction to milk. A second child was treated similarly, but he experienced a severe rash after each injection. Schlossmann felt that one could determine whether or not a child had ever been fed cow's milk by his reaction to calf or beef serum, assuming that prior contact with milk would render the child unreactive to the animal serum. He also felt that one could accustom a child to cow's milk by the subcutaneous injection of beef serum.

From these early observations followed a series of reports in which the discussion of the mechanism of the severe reactions was bitterly contested. In many instances the associated factors of a severe debilitating and nutritional disorder, or what appears to be infectious diarrhea, plus the variety of methods of preparation of the artificial cow's milk formula, make the interpretation of the cause of trouble with the formula somewhat difficult.

Talbot's[54] paper in 1916 on "Idiosyncrasy to Cow's Milk: Its Relation to Anaphylaxis" called attention to this syndrome in the American literature. Park[34] in 1920 described an infant who had the type of anaphylactic reaction previously reported. The infant had been breast fed until the age of 6 weeks, at which time he was given his first feeding of cow's milk. He immediately vomited, and became drowsy, pale and prostated. A scratch test was negative at 12 weeks, but immediately after this the child appeared to have a generalized reaction characterized by drowsiness and loose stools. An intradermal test was performed 3 days later with delayed production of an anaphylactic shock. Some time after this symptoms again recurred, this time 3½ to 4 hours after cows' milk ingestion. By 6 months of age the infant was successfully weaned to goat's milk, but the cow's milk sensitivity still persisted at 20 months of age.

Glaser[19] reports on an infant who had alarming angio-edema shortly after a few feedings of cow's milk formula. He also discusses 2 patients of Kerley's,[26] one of whom died in shock within a few minutes after forced feeding of cow's milk, and another infant who narrowly escaped death from anaphylactic shock when 7 drops of milk were placed on the tongue.

More recent reports of acute severe reactions to milk are those of Valléry-Radot and Blaumontier[56] and Collins-Williams.[7] Metabolic studies of 2 infants with shocklike

allergic reaction after feeding cow's milk were made by Crawford et al.[9] in which they found diminished circulatory volume, and an increase in extracellular fluid volume at the expense of intracellular fluid. There was a small external loss of sodium and water, with intracellular accumulation of potassium at the height of the disturbance. ACTH, cortisone and DOCA failed to protect the patients from milk reaction, whereas sodium lactate and chloride did protect.

SYMPTOMATOLOGY

The majority of the reports on the symptomatology of cow's milk allergy in recent years concern themselves with the milder reactions, and with a discussion of the mechanism of sensitization. From a variety of sources, it is apparent that the more commonly encountered symptoms which have been attributed to sensitivity to cow's milk are found in the first year of life. Those reported include refusal of milk, spitting up, vomiting after milk feeding, obvious signs of abdominal pain, colic, diarrhea,[10] bloody stools, constipation, failure to gain.[57] Symptoms referable to the respiratory tract include excessive mucus in the nose or throat, laryngeal spasm, croup and wheezing. Others which have been described are general irritability with restlessness, persistent crying, excessive hunger, drowsiness or wakefulness. Skin rashes of various types, particularly eczema and urticaria, and infrequently purpura are reported due to milk allergy. Fever is infrequently ascribed to milk sensitivity. It will be seen from this gamut of symptoms that practically all body systems have been incriminated as the reacting organ in certain instances of alleged milk sensitivity.[6] It is also apparent with this protean symptomatology that many instances of allergy to cow's milk are readily confused with other diseases, and, conversely, considerable doubt has been cast upon the allergic origin of illness actually due to hypersensitivity in specific patients. None of the symptoms which have been detailed are pathognomonic of sensitivity to milk, nor are they peculiarly related to allergy per se. For this reason the proof of their relationship to cow's milk as an etiologic factor, or as the only etiologic factor, is essential. Many of the reports in the literature fail to bring out this point with clarity. Nevertheless, the growing experience with feeding of infants and older children with cow's milk makes it seem that any one or several of these symptoms in combination can be present and are often due to milk sensitivity. However, the uncritical implication that, if any of these is present, then allergy to cow's milk indeed must be present, has had a damaging effect on the acceptance of an allergic basis for any illness in infancy or childhood in certain quarters.[36]

DIFFERENTIAL DIAGNOSIS

From the foregoing it is clear that in the differential diagnosis in an infant or a child in whom milk allergy is suspected, one must consider

a variety of other conditions. The one in which the differentiation may be most difficult, because improvement clearly follows elimination of milk and thereby lactose from the diet, is *galactosemia*.[80] The typical symptoms are gastrointestinal disturbance, such as diarrhea, vomiting or abdominal distention, with malnutrition. Hepatomegaly, jaundice and splenomegaly are often present, and, as the condition progresses, lamellar cataracts and mental retardation may appear, ultimately ending in death in early infancy. Tests for galactose in the urine and blood galactose and glucose tolerance curves should be carried out while the child is receiving cow's milk. This is a relatively rare condition, but it is possible that mild forms compatible with longer life may occur.

Pyloric stenosis, with its classic symptoms of projectile vomiting, coming on usually by about four to six weeks of age, primarily in male infants, may give rise to the suspicion of milk allergy. This confusion is more likely in the infant in whom there is pylorospasm without the presence of the typical palpable tumor at the pylorus and in whom the vomiting is not quite so persistent as in true pyloric stenosis.

Other conditions which should be considered in the infant with diarrhea and nausea, vomiting and colic, are acrodynia and hypophosphatasia.[14] The latter has been relatively recently recognized. Infants who have *hypophosphatasia* have an abnormal mineralization of bone, a decreased alkaline phosphatase in the serum and tissues generally, and an increase in the blood and the urinary excretion of phosphorylethanolamine. Serum calcium is normal or slightly increased in these infants. Hypophosphatasia is thought to be inherited as an autosomal recessive, and the prognosis is poor if the onset of the condition occurs in the first few months of life.

Any of the gastrointestinal disorders of infancy may have features in common with allergic reactions in the gastrointestinal tract. These may represent a range from low grade enteric bacterial infections to monilial infections which would be altered in their course by changing the intestinal flora by changing the type of milk fed to the child. Malformations of the gastrointestinal tract and the malabsorption syndromes all may have many points of resemblance to milk allergy.

The infant who presents a combination of gastrointestinal and respiratory symptoms at an early age requires investigation for the presence of fibrocystic disease of the pancreas. Respiratory symptoms alone due to milk sensitivity are less commonly seen in early infancy than combined with other symptoms, but they may resemble acute respiratory infections or more chronic infections of the respiratory tract, such as acid-fast or fungal infections. The differentiation between laryngeal spasm due to allergic edema, due to flaccid epiglottis, and to malformations of the upper and lower respiratory tracts often is difficult, and organic lesions should be sought for carefully before attributing symptoms to milk sensitivity.

The skin lesions typical of infantile eczema ordinarily cause little confusion, and frequently are the major manifestations of milk sensitivity. On the other hand, there are many rashes in early infancy which are due to nonallergic causes; to inherent peculiarities in the infant's skin, such as mild ichthyosis or even ectodermal dysplasia, local irritation, and contact dermatitis, which may need differentiation from rashes due to ingestion of milk.

Symptoms which involve other body systems, such as the nervous system, require recognition and differentiation from congenital malformations and birth injuries of the central nervous system.

Perhaps the most common single cause of illness wrongly attributed to cow's milk allergy is poor feeding practice, which may give rise to many of the milder complaints which have been listed. These poor feeding practices can be detected only by a careful detailed history as to the amount of foods, the manner in which the infant is fed, and the frequency, as well as the amount, of handling to which he is subjected.

DIAGNOSIS OF MILK ALLERGY

As was indicated in the history of the recognition of allergy to cow's milk, there has been considerable confusion and discussion about the techniques for diagnosing this condition. Obviously, the diagnosis rests primarily on clinical grounds, and each clinician has his own, somewhat different, standards of diagnosis. If one insists upon the presence of one or more of the classic allergic diseases or disorders such as eczema, urticaria, noninfectious rhinitis, and asthma caused by cow's milk, relatively few infants will have milk allergy. In fact, the full-blown picture of these allergies may not be manifest for any cause until well beyond infancy and early childhood. If one accepts as early infantile allergic reactions the many other symptoms which may be evanescent, which have been detailed above, we find that there is much latitude in the diagnosis of sensitivity due to cow's milk. We need, therefore, other objective means for diagnosis. At the age in which milk allergy is frequently first encountered, namely up to two years of age, the standard skin-testing techniques by scratch or intradermal methods may give either falsely negative or falsely positive reactions to milk as well as to other allergens which demand discrimination in interpretation. This is particularly true in the first few months of life, when one may see nonspecific reactions, or unreactivity of the skin.

In a series of 109 allergic infants from 3 months to 2 years of age, scratch tested to milk, we found 24 (22 per cent) with both positive test and clinical sensitivity to milk, 9 (8 per cent) with clinical allergy and negative scratch test.[3] There were 13 infants (11 per cent) with positive scratch tests and no clinical evidence of milk allergy at the

time they were examined. These children all fell in the age group between six months and two years. In a smaller group of children (41) under 1 year of age who were referred for allergy, but who ultimately proved to have no allergy, scratch tests to a variety of allergens, including milk, were positive in 24 of 41 tested.

Hill[24] reports a series of 63 children with a negative scratch test to milk, of whom 56 per cent reacted with a positive intracutaneous test to cow's milk. He feels that a positive scratch test to milk is almost always indicative of clinical sensitivity, whereas a positive intracutaneous test may or may not be.

A more detailed analysis of skin reactions to milk in allergic children is found in papers by Ratner, Crawford and Flynn,[38] and by Ratner and Collins-Williams.[37] In the first report an incidence of 28 per cent positive scratch tests to milk was found in 64 infants and preschool children. In the second paper, confined to a study of infantile and childhood eczema, 26 per cent of 42 infants and 16 per cent of older children had positive scratch tests to cow's milk. They include a review from the literature of reported skin test reactions to milk in eczema with a percentage ranging from 5 to 48.

From these few examples we can see that direct skin testing for cow's milk sensitivity is a useful, but not an entirely satisfactory, infallible, technique for diagnosing clinical sensitivity.

It is frequently possible to detect passively transferrable antibodies in an infant's serum. This is a technique which has a great deal of value, but is applicable in selected cases only, because of the difficulty of routinely obtaining sufficient quantities of blood from infants, and finding suitable recipients. Here again there is often lack of complete agreement between clinical sensitivity and positive tests. In one study false negatives and false positives were found in approximately one fifth of the tests.[5]

The presence of eosinophilia in the stools has been suggested as an objective sign of food sensitivity, including milk allergy.[33, 45] It is my personal opinion that, though this may be helpful if present, and is undoubtedly present in some instances, in many more cases of definite proved allergy the stools contain no eosinophils. Therefore, in my experience, this is not as practical a routine method as it might appear on the surface.

At present there are no simple clinical techniques for carrying out any human antibody titrations to milk in vitro in any fashion. This is one of the problems which could profitably be explored in the laboratory.

The diagnosis of milk allergy, therefore, rests largely on clinical grounds with some confirmatory evidence from skin tests. Most observers tend to accept an allergy to milk if the infant's symptoms occur on the introduction of milk, disappear when it is removed from the

diet, and recur with its reintroduction, if this sequence of events can be repeated on several occasions under relatively controlled conditions without subjecting the child to any life-threatening or alarming symptoms. Obviously, the simple dietary approach is one which is hardly scientific, and one in which there may be many factors other than allergy involved. Galactosemia points up this fallacy in the clinical approach of using elimination of milk as the sole basis for making a diagnosis. The increasing use of heat-treated or acid-treated and evaporated milks in infant feeding has changed the type of allergen to which these children are exposed in a very radical fashion from that which was the common allergen in the early days of artificial feeding. This may well account for a decline in the number of positive skin tests to milk reported in the more recent literature, and may indeed be a reflection of a true decrease in antigenicity of and allergy to this particular food.[37] The ultimate diagnosis of an allergy depends in part upon the amount of milk necessary to produce symptoms. One can suspect that allergic symptoms will follow the introduction of relatively minute amounts of milk, whereas those which are due to chemical intolerance of milk or to some extraneous proteins or other factors in milk will require larger amounts in order to manifest themselves.

INCIDENCE OF COW'S MILK SENSITIVITY

Like sin, the incidence of cow's milk sensitivity will vary with the observer, his criteria and his population sample. In our series[2] of 304 unselected well babies under 2 years of age who were formula fed, there were 4 (1.3 per cent) who we felt met conservative criteria for clinical allergy to cow's milk. On the basis of similar criteria for the presence of allergy, but in a larger group of 3000 patients from his pediatric practice which included older children and excluded allergy referrals, Collins-Williams[8] found 9 (0.3 per cent) with clinical sensitivity to milk. Loveless[29] reported an incidence of 1.5 and 2.3 per cent in 2 large series collected by questionnaire from data from more than 300 physicians, in a general population survey. When one considers that allergy of all types may affect 10 per cent of the general population of all ages, if allergy to cow's milk were in truth present in even 1 per cent of rather large child and adult groups, this is an impressive number of persons presumed to be sensitive to one specific food. In other terms, one could calculate in this country of more than 160 million persons that approximately 1,600,000 might be allergic to cow's milk. There is always danger in making sweeping generalizations from mathematics, but these numbers give one some idea of the importance of this problem.

Considered from the point of view of allergy to milk in the allergic population, the incidence which has been reported by various authors

is obviously much higher. Milk sensitivity is found in 7 per cent of Clein's[6] practice, and Glaser[19] estimates a similar rate among his allergic child patients. In the study which Bachman and I[3] conducted on the incidence of allergy to cow's milk among allergic infants under 2 years of age, as a parallel to its incidence in so-called well-babies, we found 30 per cent (33) of 109 allergic babies who were clinically sensitive to cow's milk. Thirty-seven of these children gave positive scratch tests to milk.

It should be re-emphasized that one would gain a different idea of the incidence of allergy to cow's milk if he considered primarily the results of positive skin tests to milk among allergic persons of different ages. By referring again to Ratner and Collins-Williams'[37] recent report on the incidence of positive reactions to milk among 42 infants with eczema, 26 per cent reacted positively to the milk scratch tests, milk ranking tenth in order of frequency of positive allergy tests. In the 38 children with eczema 10 per cent had positive tests to milk, or thirteenth in order of frequency. The studies by many other physicians on eczema, including Hill and Sulzberger,[22] Sulzberger and Wolf,[53] Urbach,[55] Feinberg,[12] include milk, with egg and wheat among the most common dietary causes of eczema, the rank assigned to each food varying with different observers.

This review of the incidence of cow's milk allergy points up some of the many variables one encounters in trying to arrive at an objective opinion about the frequency of sensitivity to this particular food. When the substance itself varies from cow to cow, and the mode of preparing it differs with each producer, irrespective of the multitude of inconstant factors added by both the patients and their physicians, it is little wonder that conflicting opinions arise. They can be resolved only when an objective test for milk sensitivity can be applied under controlled conditions to statistically significant comparable groups, described with sufficient detail to permit verification by several observers.

IMMUNOLOGY

The need for an understanding of the basic mechanism of milk intolerance has given rise to many immunologic studies of milk. The earliest clinical reports offered various theories often largely based on speculation as to whether unaltered protein traversed the gastrointestinal wall and under what conditions. These are reviewed in an extensive bibliography by Ratner and Gruehl[42] in 1934 in their study of the passage of natural protein through the normal gastrointestinal wall. They showed by guinea pig experiments that at least 50 per cent of both young and adult animals were sensitized to milk by feeding and could be shocked by an intravenous challenging dose of milk. They also discuss the

development of positive intradermal skin tests and passive transfer tests in human volunteers. Previous to these studies, in 1923 Schloss and Anderson[46] demonstrated that the blood of most "marasmic" infants contains precipitins to cow's milk, and the serum in many cases would passively sensitize a guinea pig.

Permeability of the gastrointestinal tract in infants to milk and other proteins was one of the first points demonstrated by precipitin tests and anaphylaxis experiments in human beings and animals by Schloss and Worthen,[47] Wells and Osborne,[58] Anderson et al.,[1] DuBois et al.,[11] Lippard et al.[28] and many others. Then followed a dearth of interest in this aspect of milk sensitivity until it was reinvestigated by Berger[4] in 1953, who showed complement-fixing antibodies to milk in 20 of 84 children, 7 of whom were allergic. Tagged egg albumen was used by Gruskay and Cooke[20] in 1955 to demonstrate that appreciable amounts of this material were absorbed in normal infants and an even higher amount in those with diarrhea.

The human gastrointestinal tract is also permeable to bromide, iodides, heavy metals, cascara, sulfonamides, penicillin, snake root and ragweed protein which are secreted in milk, and may be present in concentrations which will produce symptoms on ingestion. The question of the absorption of antibody formed in the cow's udder, by human beings drinking such "immune milk," has recently been investigated by Peterson and Campbell and awaits confirmation.[35]

From these studies attention was then turned to the nature of the milk protein itself. A mass of evidence accumulated from the study of the fractions of milk, casein, lactalbumin and lactoglobulin, indicated that they were antigenic and capable of producing anaphylactic reactions in both animals and man.[42, 43] The initial observations that casein is relatively heat stable, while lactalbumin and globulins are heat labile have remained valid,[27] even though some of the recent refinements of chemical analysis have cast doubts upon the purity of the fractions used in the early studies. The species specificity of various mammalian milks showed a definite similarity, if not identity, between the caseins, with distinction between the whey proteins.[23]

A logical step from the discovery of the heat lability of the lactalbumin and lactoglobulin fractions was the study of the effect of heat on the antigenicity of whole milk. Ratner and Gruehl[43] were among the first to call attention to the loss of antigenicity of boiled, evaporated, acidified evaporated milks, which they ascribed to alteration of whey protein by moist heat. Since they were unable at that time to obtain lactoglobulin free of lactalbumin, their studies were done primarily with lactalbumin and casein. The importance of this work cannot be overestimated, since it gave added impetus to the use of heat-denatured milk for infant feeding.

These studies have been reviewed recently by Ratner's co-workers, using specially prepared protein fractions, of alpha casein, beta lactoglobulin and alpha lactalbumin, which have been shown by electrophoresis to be pure fractions.[39, 40, 41] Using these purified fractions, they find that milk contains 60 per cent alpha casein, 11 per cent beta lactoglobulin and 2.4 per cent alpha lactalbumin. Using antigen solution of comparable nitrogen content, they report on a series of guinea pig experiments which show that the fractions are immunologically distinct. Beta lactoglobulin is the most allergenic, by both the intraperitoneal route and by oral feeding to produce sensitization. This is in contrast to Ratner's earlier studies, with less pure fractions, in which lactalbumin was thought to be the more significant protein. Heat denaturation destroys the allergenicity of alpha lactalbumin, but not that of alpha casein, and decreases the allergenicity of beta lactoglobulin for guinea pigs when given either orally or by intraperitoneal injection. Reactions occurred with heat-denatured whole milk only in animals sensitized to alpha casein, which is heat stable, and probably but slightly altered, if at all, by heat. For this reason they propose that heat-denatured milk is probably safe for milk-sensitive persons except those very sensitive to alpha casein.

TREATMENT

This leads us to consideration of the management and treatment of milk allergy. Here the basic tenets of allergy apply: avoidance of the noxious substance; alteration of the material to make it innocuous; or development in the patient of a tolerance of or desensitization to the agent. All these methods are in current use. The vigor with which they are carried out will depend upon the individual problem.

In some instances milk is simply left out of the diet, often spontaneously by adults or children who are given free choice of diet. The hazard of insufficient caloric, nutrient and vitamin intake is obvious if adequate replacement is not made. When it is, and the diet is kept well balanced in spite of the omission of milk, this is not incompatible with good health with allergy symptoms eliminated. More frequently one must find a substitute for cow's milk for nutritional reasons for cow's milk-allergic persons. Here one has a choice depending upon the age of the patient, degree of sensitivity, and economic status, which ranges from foster mother's breast milk or goat's milk, modification of cow's milk, to nonmilk substitutes. Breast milk banks and wet nurses are almost nonexistent in this country at present, and therefore this is costly and rarely necessary. The use of raw fresh goat's milk is being supplanted by evaporated (Meyenberg) or dried (Dale—Cutter) goat milk, and for the child who is not sensitive to casein this offers a satisfactory substitute.

TABLE 15. *Composition of Milks*

TYPE OF MILK	PER CENT				ADDED VITAMIN D PER QUART USP UNITS	DILUTION	CALORIES PER FLUID OUNCE
	F	P	C	Ash			
Human	3.8	1.1	7.0	0.21			22
Cow:							
Whole	4.0+	3.3	5.0	0.72			20
Evaporated	3.6	3.2	4.5	0.7	400	1:1½	20
Dried (½ skim)	1.5	4.25	5.5	0.9		IT:1 oz. (fl.)	16
Goat:							
Whole	3.5+	3.1	4.6	0.79			20+
Meyenberg evaporated*	7.0	15% solids				1:1	20+
Dried	26.75†	26.5	38.0	6.5		1 oz.:7 oz. (fl.)	20
Dried (Dale)**	27.0†	26.0	38.0	6.5		1 oz.:10 oz. (fl.)	14

* Meyenberg, San Francisco.
† Dry powder.
** Cutter, San Francisco.

The many modifications of cow's milk which alter the native raw milk protein include pasteurized, boiled, evaporated, dried, and modified milk to resemble human milk in percentage composition, or acidified to alter the whey protein, and to make curd more digestible.

Derived from cow's milk is a formula consisting of amino acids from the enzyme digest of casein (Nutramigen), with added carbohydrate as Dextri-Maltose and minerals, to have a composition close to human milk. This is easily assimilated by most infants as a nonallergic food. It also is utilized by patients with mucoviscidosis, celiac disease and galactosemia because of its lack of the various factors which these patients cannot metabolize. This should be kept in mind when using it as a test diet in drawing conclusions which have diagnostic import.

The other nonmilk substitutes in most common use in this country are formulas derived from soybean flour. These are obtainable in both powdered and liquid forms. The slight variations in the two forms are often sufficient to make one or the other superior for an individual baby. The nutritional virtues of vegetable protein are contested with considerable heat by certain students of infant nutrition, who feel that they lack elements present in animal protein,[15] and also may be goitrogenic.[52] In my own experience I have never encountered the latter reaction in an infant receiving soybean milk and have been unable to find sufficient information in the literature to document this alleged side reaction in a way which would deter me from the use of this milk.

TABLE 16. *Composition of Milk Substitute Formulas*

TYPE OF FOOD	PER CENT				ADDED VITAMIN PER QT. USP UNITS			DILUTION	CALORIES PER FLUID OUNCE
	F	P	C	Ash	A	D	B*		
Amino acid:									
Nutramigen†	2.7	2.2	8.5	0.6	2500	400	+	1 measure:2 oz. (fl.)	20
Meat base:									
Gerber‡	3.9	3.4	4.9			400	+	1:1	21
Soybean:									
Mull-Soy Liquid§	4.0	3.1	4.5	1.0				1:1	20
Mull-Soy Dry§	4.0	3.1	4.5	0.9				1T:2 oz. (fl.)	20
Sobee Liquid*	2.6	3.2	7.7	1.0	2500	400		1:1	20
Sobee Dry*	2.6	3.2	7.7	1.0				6T:7 oz. (fl.)	16
Soyalac Liquid‖	4.0	2.0	6.0				+	1:1	20
Soyalac Dry‖	3.67	3.25	6.2					1 oz.:7 oz. (fl.)	20

* B complex added = B+.
† Mead Johnson, Evansville, Ind.
‡ Gerber Products, Freemont, Mich.
§ Borden Rx Products, New York City.
‖ Loma Linda, Arlington, Calif., and Mt. Vernon, Ohio.

TABLE 17. *Composition of Hypoallergenic Milk Formulas*

TYPE OF FOOD	PER CENT				ADDED VITAMIN PER QT. USP UNITS				DILUTION	CALORIES PER FLUID OUNCE
	F	P	C	Ash	A	D	C Mg.	B		
Baker's*	3.3	2.2	7.0	0.7	2500	800	50	+	Liquid 1:1 Pwd. 4 oz.:1 qt.	20
Similac†	3.4	1.72	6.55	0.5	2500	400	50	+	Liquid 1:1 Pwd. 4 oz.:1 qt.	20
SMA‡	3.5	1.5	7.0	0.38	5000	400	50	+	Liquid 1:1 Pwd. 4 oz.:1 qt.	20
Hypoallergenic whole milk powder (Wyeth)‡	3.5	3.3	4.7						4T:8 oz.	20

* Baker's Milk, Cleveland, Ohio.
† Ross Laboratories, Columbus, Ohio.
‡ Wyeth, Philadelphia.

TABLE 18. *Ingredients in Milk Substitutes*

INGREDIENT	MODIFIED MILKS			SOYBEAN FORMULAS			NUTRAMIGEN	MEAT BASE
	SMA	Similac	Baker's	Mull-Soy	Sobee	Soy-alac		
Protein:								
Milk (nonfat)	+		+					
Casein (mod.)		+						
Soybean				+	+	+		
Amigen							+	
Beef heart								+
Carbohydrate:								
Sucrose				+	+	+		+
Lactose	+	+	+					
Dextrins, dextrose maltose			+	+	+	+	+	
Fat:								
Beef	+							
Milk							+	
Soy	+			+	+	+		
Corn	+	+	+					
Sesame								+
Cocoanut	+	+	+		+			
Olive		+				+		
Miscellaneous:								
Lecithin	+			+				
Carrageen (chondrus)	+				+			
Arrowroot flour							+	
Tapioca								+
Cocoa butter		+						
Brewer's yeast							+	
Minerals:								
KH(CO_3)	+							
Calcium	+							
Iron	+		+			+		
Potassium citrate		+						
Calcium phosphate				+				+
Ca(OH)$_2$				+			+	
Sodium chloride				+				+
Calcium carbonate					+	+		
Dicalcium phosphate					+	+		
Calcium gluconate							+	
K dihydrophosphate							+	
K_3PO_4							+	
Potassium chloride							+	
Calcium citrate								+
Iron sulfate							+	
Magnesium peroxide							+	
Vitamins added:								
A	+	+	+		+		+	+
B	+							
B complex		+	+			+	+	+
C	+	+	+					
D	+	+	+		+		+	+

The history of the development of soybean formula is sketched by Glaser.[19] It was introduced as a cheap substitute for breast and cow's milk in China in 1929 by Tso. Hill and Stuart perfected a practical formula for soybean milk in 1929, which is commercially available as Sobee. Shortly thereafter Mull-Soy was introduced. Several other soybean milks are now available, including Soyalac (Soyagen). These are obtainable in both liquid and powdered forms.

The most recent addition to the list of substitutes is meat-base milk, based on a formula devised by Rowe, which has since been modified by several others, and is available commercially. This is often well accepted by the older child and the infant, who may find it difficult to adjust to the flavor of Nutramigen or soybean milk. All the substitutes for milk may have some side reaction in certain children, such as diarrhea, buttocks irritation or, less often, constipation. As technology progresses we will undoubtedly have additional balanced milk substitutes, but these are the major ones in use at present.

One additional method of treating milk allergy is the deliberate oral feeding of minute amounts of milk with gradually increasing doses, a method utilized by the first physicians recognizing milk allergy. The strength of the mixture, and its rate and amount of increases per day, will, of course, be determined by the severity of the allergy. For a child who has had an anaphylactic reaction to a few drops of milk, an infinitesimal dilution would be used initially. For one whose allergy is of milder degree the first feeding might be in the range of 5 to 10 cc. of undiluted milk with more than one feed per day. A schedule which could be used as a general guide is shown in Table 19.

One other technique which aims at modifying the reaction within the patient himself is the use of Propeptane,* an enzyme hydrolysate of milk, broken down to a theoretical level of propeptones. If this ma-

* Delare Associates, Phila., Pa.

TABLE 19. *Schedule for Oral Desensitization to Milk*

MILK	WATER	DAILY DOSE OF MIXTURE	DAYS
5 cc.*	1000 cc.	5 cc.	6
5 cc.	500 cc.	5 cc.	6
5 cc.	250 cc.	5 cc.	6
5 cc.	125 cc.	5 cc.	6
5 cc.	60 cc.	5 cc.	6
5 cc.	30 cc.	5 cc.	6
5 cc.	15 cc.	5 cc.	6
5 cc.	7.5 cc.	5 cc.	6
5 cc.	5 cc.	5 cc.	6†

* 5 cc. = 1 teaspoonful; 1000 cc. = 1 quart.

† After 59th day give 5 cc. of undiluted milk daily. Gradually increase the amount as tolerated. Reactions—nausea, abdominal pain, diarrhea, eczema, urticaria, asthma, etc.—require reducing the dose.

terial in capsule form is given exactly one-half hour before ingestion of the allergenic food, it is thought to react as a haptene to bind any circulating antibody, and thus prevent a union of the antibody and milk antigen which might be absorbed when the milk is ingested shortly thereafter. By this means it is assumed that one can gradually increase the amount of ingested milk while decreasing the Propeptane, until the patient is taking milk (or other food so blocked) without reaction. This was a method used by Urbach[55] with success; in our hands it has not given consistent results in either infants or children.

Mention should be made of Glaser and Johnstone's[16, 17, 18] report on the prophylaxis of milk allergy in the siblings of allergic children by the use of soybean formula from birth until near or after one year of age. They report a significant decrease in the percentage of allergic diseases developing in patients in the experimental groups, with four times higher incidence of allergy in allergic siblings fed cow's milk from infancy over the experimental group receiving no cow's milk during their first year of life.

The statistics of this work have been challenged by Lowell,[30] but since no comparable study extending for this period of time is yet available for comparison, it would seem that the principle of prophylaxis of cow's milk allergy by substitute feeding should be given careful consideration in the type of family selected by Glaser. (See also p. 901.)

SUMMARY

Cow's milk allergy is a very real problem which has developed in the current century along with our advances in infant feeding. It is part of the price we must pay for salvaging many infants by artificial formula whose natural source of nourishment has failed. It is of minor and negligible importance compared with the toll which diarrhea and nutritional disorders took in the pre-Pasteur days. From all indications the incidence of sensitivity to cow's milk may be declining, owing to a decreasing antigenicity of processed milk products. The severity of the symptoms of hypersensitivity may also be declining because of modification of milk proteins. In spite of this there still remains a significant number of children who have unquestionable allergic reactions due to early sensitization to cow's milk, and for them their trouble is not negligible. This presents a hazard to them in infancy, and may become a major inconvenience in later life. We need to re-examine the entire problem of milk allergy with our new tools of immunochemistry, not only to determine the nature of all the reacting substances and their mode of action, but also to obtain leads for early rational diagnosis and intelligent management. Our greatest challenge now is not to make a "sacred cow" out of cow's milk allergy.

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THE PROPHYLAXIS OF ALLERGIC DISEASE IN INFANCY AND CHILDHOOD

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It is generally recognized that the human infant, upon leaving the uterus at birth, must develop immunity against exposure to infection, which starts when the first microorganisms enter the body with the first breath of air and with the first swallows of water or food. It is not generally appreciated, however, that the newborn infant must also develop protection against possible injurious effects of foods, as well as other nonliving substances. The mechanism of this, which is by no means as well understood as that which protects against infection, is probably part of the general mechanism of actively acquired immunity, using the term "immunity" in a broad sense, which protects the individual against all potential noxious agents. Exposure to many of these starts as soon as the infant emerges from the birth canal, and even before, since the placenta is permeable to a great variety of substances.

In the case of infections, the newborn infant has some degree of passive immunity for a time because of maternal antibodies which passed the placenta and entered the fetal circulation. Thus the newborn infant is not rapidly overwhelmed by the microorganisms which must accompany him, one might almost say, as symbiotic parasites for the rest of his life, and as the maternal antibodies disappear he gradually develops his own active antimicrobial defenses. In a parallel manner, nature protects the newborn infant against the potentially noxious effects of food by providing human breast milk, the only natural food for the newborn

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human infant. A little reflection will convince anyone that this is not the case with cow's milk, since it is obvious that the cow, even after thousands of years of domestication, still makes milk primarily designed for calves and not for the newborn human infant. However, though cow's milk is not a natural food for the newborn human infant, it certainly is a natural food after the newborn period has passed, and of the foods it may well be said to be nature's greatest gift to mankind.

Thus it seems evident that, so far as protection against possible injurious agents during the first few months of life, when the infant is adapting to an extrauterine environment, is concerned, there are two mechanisms involved. The first protects against infections by means of immune bodies from the mother which pass the placental barrier and protect the infant until active immunity against infection is acquired. The second mechanism, human breast milk, provides the infant with a "natural food" as a source of nutrition during the transition period of adaptation to the foods which must sustain him after weaning. Almost any food and many drugs which the mother ingests pass immunologically unaltered to the infant in minute amounts with the breast milk.[24] This would seem to be a wise provision of nature to accustom the infant gradually to minute amounts of almost anything it might be exposed to in the way of ingestants in later life. Thus "active immunity," so to speak, for protection against foods is acquired at the same time the infant is acquiring active immunity against microorganisms. Just how long the infant should continue on the breast appears to be answered by nature by the fact that in the average infant the first tooth erupts between the ages of six and seven months.

FOOD AND THE DEVELOPMENT OF ALLERGY

Most allergies in early infancy are due to food, perhaps because the gastrointestinal tract of the newborn infant is the most complicated in structure and function of the three groups of tissues which separate the newborn individual from the environment (the others being the skin and the respiratory tract). These are the tissues which obviously must suffer the greatest initial stress of the conflict which results from the effort of the infant to adapt to extrauterine life.[31]

Cow's Milk

Of the foods which produce allergic reactions in infancy and childhood, cow's milk is the chief offender, probably both because cow's milk is the first foreign protein commonly fed after birth and because it is practically the only food to which the infant is exposed at this early age, so that the exposure is truly overwhelming. Hill* has pointed out the

* Personal communication.

enormous amount of protein, especially milk, which the infant ingests in proportion to body weight. A child of 9 kg. (20 pounds) commonly takes a liter of whole milk a day (30 to 40 gm. of protein). This would correspond to about 8 liters of milk for a 75-kg. adult. Since immunologically unaltered protein may pass the intestinal wall at all ages,[54] the infant certainly absorbs into the blood stream a relatively considerable amount of cow's milk protein, which, as a food, has a relatively high sensitization potential. Not only is cow's milk the food most commonly responsible for allergic diseases in early life, but also, according to Alvarez and Hinshaw,[2] it is one of the most important causes of food disagreement in later life. It seems reasonable to assume that this, in many instances, is a direct continuance of a frank or latent allergy to milk which started in early life.

Fries[18] pointed out the obvious fact that there are several kinds of disagreements to foods which are not of allergic origin, and therefore rejects the thought that the disagreements to cow's milk described by Alvarez and Hinshaw[2] are, for the most part, allergic. This is a difficult subject to discuss because there have been, and still are, no generally accepted exact definitions of, and the differences between, allergy, idiosyncrasy and hypersensitivity to food.

To limit the definition of an allergic reaction to one in which union of antigen and antibody can be unequivocally proved is not satisfactory because there are many reactions (particularly to some drugs) which have most or all of the characteristics of allergic reactions in which such a union has not been demonstrated. In some which were originally in this category new methods have proved an antigen-antibody reaction. Full elucidation of this subject is beyond the scope of this presentation.

The rapidity with which the newborn infant can develop tolerance for food is clearly indicated by the fact that about 30 years ago the custom was introduced of feeding infants raw egg yolk at the age of 3 months. It was soon found that a great many infants had rashes, gastrointestinal disturbances and other manifestations of allergy to egg when it was introduced at this early age, so that this practice was almost universally discontinued. Egg yolk is not now introduced by most physicians until the ages of six to nine months, when it is commonly tolerated without difficulty.

Immunologically unaltered egg protein can pass the intestinal barrier at all ages.[54] Immunologic processes which occur on the feeding of new foods to very young infants, as reviewed elsewhere,[23] as well as experimental studies in animals (guinea pigs) by Wells and Osborne,[53] suggest that the tolerance developed to egg protein is immunologic. *This observation that the infant in most instances naturally acquires immunologic protection against the harmful effects of allergy to egg somewhere between the ages of six and nine months was the starting point of our work.* The thought occurred that if infants could be started

on some food other than the traditional cow's milk during this period of physiologic immunologic immaturity, allergy to cow's milk, which is responsible for most of the allergic phenomena of early infancy[10, 38] and particularly for atopic dermatitis, [3, 16] might be minimized or even prevented.

Abt,[1] in 1912, made the observation that practically since the beginning of clinical observations on the feeding of infants it was recognized that for some unknown reason there were some infants with whom cow's milk disagreed. He reviewed the theories about this and noted that the harmful effects of feeding cow's milk in such infants could not be explained on the basis of disease of the digestive tract or loss of physiologic function. About 25 years later Brennemann[9] stated: "The milk of every mammal is specific for its young. To this, man is no exception. There is, furthermore, evidence that the milk of one mammal is not only imperfectly adapted for the young of other mammals, but that there is even something harmful in non-specific milk. The essential nature of this specificity is unknown. While it may eventually prove to be largely, or wholly, a matter of chemistry, there is reason to believe that there is also an intangible biological factor." It is the thesis of this presentation that Brennemann's statement is correct, that the intangible biologic factor which he foresaw over 20 years ago is allergy, and, moreover, that a practical application can be made of this observation which will go far towards alleviating the scourge of allergic disease in human infants and children.

Breast Milk versus Cow's Milk

Little has been published on the effects of breast milk as opposed to cow's milk on the development of subsequent allergic disease. Grulee and Sanford[36] reported that seven times as many bottle-fed babies had eczema as breast-fed babies. Kimball and Jorgensen[40] many years later found about eight times as much eczema in the bottle-fed baby as compared with the breast-fed baby. Our studies[33] indicated that infants fed cow's milk from birth had atopic dermatitis four times as often as infants fed soybean milk from birth. If all these figures are correct, breast milk would appear to be about four times as effective as cow's milk and twice as effective as soybean milk in the prevention of atopic dermatitis.

Since, as previously stated, almost any food ingested by the mother may appear in the breast milk and cause an allergic reaction in a child sensitive to that food, the lactating mother is advised to be on a diet low in those foods known to have high sensitization potential, such as egg and cow's milk, and to eat a variety of other foods so as to avoid the risk of sensitization to any food which might be eaten in excess.

Although the evidence that a child can be sensitized in utero to foods eaten by the mother, as suggested by Ratner[46] and Ratner and Greenburgh,[48] is not conclusive, as elsewhere reviewed,[22] it can do no harm and may possibly be helpful to have the mothers of potentially allergic infants on this same diet during pregnancy. At this point it is well to mention that though all human infants are potentially allergic, for purposes of this discussion we define a potentially allergic infant as an infant who has one or more allergic parents or siblings.

Baer,[4] in discussing the prevention of allergic sensitization, has called attention to the work of Billingham and associates[5] indicating the great tolerance of very young embryonic tissue for foreign protein. Although this might offer another approach to the problem of the prophylaxis of allergic disease in the newborn, a practical method for the application of this principle has not yet been suggested.

Incidence of Cow's Milk Allergy

It has been pointed out repeatedly that the incidence of allergy to cow's milk in the general population appears to be between 1 and 2 per cent.[26] In the practice of the pediatric allergist the incidence is much higher, Clein[10] reporting about 7 per cent. Some of the difficulties of determining the incidence of allergy to cow's milk in the general population have been pointed out in previous communications.[26, 30]

It seems obvious that the answer to the problem of determining the incidence of allergy to cow's milk in the general practice of pediatrics will not be found either in well-baby clinics or allergy clinics or in the practice of the pediatric allergist. It should be found in the private practice of the pediatrician who is as interested in allergy as he is in other problems of infancy, but does not attract patients because of a particular interest in allergic infants. This has not as yet been done, but Crook and associates[12] in their study of the incidence of allergic disease in private practice have set up a model for this type of study. The pediatrician in private practice has the necessary intimate contact with the patient. The full-time academic pediatrician escapes the deluge of telephone calls and frequent house calls to which the private practitioner is accustomed; the latter picks up many clues to possible allergy, often more or less transient, which could easily escape the notice of the academic pediatrician.

Perhaps this work on prophylaxis has not been given particular attention because we tend to resent what we do not understand, as Crook[13] has pointed out in his discussion of the reasons for the neglect of allergy in pediatric practice. Certainly few pediatricians have taken the trouble to familiarize themselves with allergic diseases as they occur in very young infants and children. Most pediatricians apparently feel that it is easier, or at least more practical, to feed cow's milk preparations to the potentially allergic newborn infant and to treat the allergies symptomatically as they may arise. In fact, when this work was first presented at the American Academy of Allergy in Boston some years ago, the question most often asked was, "Why bother with all this? Why not wait until the allergies develop?" The answer to this, which the internist-allergist does not recognize, although it is an occupational disease of the internist-allergist, so to speak, to consider himself a perfectly adequate pediatric allergist, is that the principal function of the practicing pediatrician today is the prophylaxis of disease. Cer-

tainly the abundance of allergic disease in our population warrants close study by the pediatrician of anything he may be able to do for the prevention of such disease in his practice.

PREVENTION BY OTHER MILKS

We feel that the ideal method for the prophylaxis of allergic disease in the newborn is breast feeding of the infant with the mother on a controlled diet as stated above. Breast milk from wet nurses when the mother will not or cannot nurse her infant is ordinarily not practical because of expense and lack of ready availability, and there is also the objection that the diet of wet nurses cannot ordinarily be strictly controlled. The milk of animals other than the cow is usually not satisfactory because of the close, though not identical, relationships of the caseins[25] of the various mammalian milks. The use of predigested casein preparations such as Nutramigen, which undoubtedly helps in some instances, has not been satisfactory in our hands. This may be because the lactoglobulin, which may cause allergic reactions, is not completely denatured in these preparations.[14]

Meat base milks[50] are satisfactory, but relatively expensive. Lamb appears to be the most satisfactory. We were unable to feed most infants from birth successfully on pork base milk for reasons which could not be explained.* We have avoided beef base because of the close relationship between the proteins of beef and of cow's milk. Our experience with whale meat and with human blood derivatives in the feeding of the newborn is insufficient to warrant comment.

Soybean Milk. Shortly before this work on prophylaxis was started, Hill and Stuart[39] had prepared a commercially available soybean milk (Sobee—Mead Johnson & Company). It was thought that this might be a practical food on which to start a newborn infant from birth as a complementary or supplementary feeding until the infant was six to nine months of age, when cow's milk could reasonably be introduced into the diet because the period of immunologic immaturity would be past. It was felt that if this were done, any sensitivity acquired by the infant would then be to soybean and not to cow's milk. That this did not happen, however, is explained by the work of Ratner and associates.[49]† They showed that, in contrast to cow's milk, soybean protein has a low sensitization potential and that the soybean milk used for the most part in this work (Mull-Soy Liquid—Borden Company) could not be shown by animal experiments to have sensitizing properties. This is perhaps important in view of the many uses to which the soybean is now put in the American economy.

* Unpublished data.

† Personal communication from Dr. Ratner and associates.

A preliminary study was made of the feeding of soybean to infants from birth.[32] The starting formula was commonly one-third normal strength, and this was gradually increased to full strength as tolerated with the addition of other foods according to a prearranged design to assist in the prophylaxis of allergic disease.[27] At the age of one year the only difference which could be ascertained was that more of the experimental infants were over the expected weight for one year than the infants fed by the orthodox methods. To parallel this investigation, which was made in potentially allergic infants, we also carefully watched for the appearance of allergic disease as the child developed.

Our experimental group of potentially allergic infants numbered 96, of whom 88 were fed a commercially available soybean milk (Mull-Soy Liquid), 5 meat base formulas and 3 breast milk with the mother on a controlled diet. Our first control group consisted of siblings of these infants. It was found that four times as many infants in the control group had atopic dermatitis (eczema) as those in the experimental group, as stated above.

By continued observations in these children, we found, to our surprise, that only about 15 per cent of these infants had subsequent major allergic disease before the age of 6 years as compared with 65 per cent of the control series. This was of such great importance that another control series was selected consisting of 175 infants, unrelated by blood to the infants of our experimental series, whose personal and family histories were practically the same as those of the experimental series. In this group 52 per cent had major allergic disease by the age of 6 years as compared with about 65 per cent of the first control series. This is a remarkably close correlation for this type of biologic work.

It thus appears from these studies that allergic disease occurs four times as often approximately in potentially allergic children started on cow's milk from birth as in those started on a feeding other than cow's milk. The importance of this to the pediatrician, whose main interest is the prophylaxis of disease, is obvious and will be discussed subsequently.

The study here reported has received little serious consideration from pediatricians except those particularly interested in allergy. There are several factors responsible for this, the most important of which is the lack of realization on the part of those dealing with the newborn human infant that the development of allergic balance to food is a normal process which every infant must experience. If this is a fact, allergy is then a *relative* state. Only when the allergic manifestation reaches a level not consonant with accepted standards of normality does the allergy become recognizable as a clinical entity.

Another factor militating against the principles of prophylaxis here presented is the parochial characteristic of our teaching, which gives the

student the impression that cow's milk is the most nearly perfect of all substitute foods for breast milk, so that, so far as infant feeding is concerned, it has an almost sacrosanct position. This results in rejection of the concept that some substitute food other than cow's milk might be better for certain newborn infants, although most pediatricians agree that breast milk is the best food for the newborn infant.

Objections and Rebuttals

As time went on, some really valid objections began to appear.

1. First our method of controls was criticised.[43] Why did we not choose alternate cases instead of using as controls siblings in the same families? It stands to reason that the only nearly perfect control in a study of this sort would be the use of potentially allergic identical twins, using one as a control and the other as the experimental feeder. This, of course, is completely impractical, although a large group of pediatricians working together might possibly, in the course of a lifetime, hope to gather together such a series as a cooperative project. To use alternate children in the same family is also not a practical procedure. The parents will, for the most part, try this method in an effort to prevent allergies from developing only if they are familiar with the suffering which allergic disease may cause, and particularly if they have had other children who suffered from allergic disease. If this method is tried and appears effective, as it often is, they will insist on the same procedures being tried in subsequent children. If it is not effective, their interest and cooperation will be lost. The two different series of controls used in this work check remarkably well and should be adequate. This has been discussed elsewhere.[34]

2. Hill,[37] though granting that, if well tolerated, soybean milk will nourish an infant as well as cow's milk, has pointed out that soybean formulas are likely to cause diarrhea and irritation of the buttocks, which, in newborn infants, may become matters of serious concern. This is true, and the feeding of the newborn infant should be undertaken only by those well trained in this respect. When diarrhea and/or sore buttocks appeared, we endeavored to treat this in the usual manner, but, if unsuccessful, discontinued the soybean preparation. This was necessary in less than 15 per cent of the cases, including those infants in whom intractable colic or emesis also appeared to be due to the soybean feedings. However, the greater part of this work was done with one of the older preparations of soybean milk, and since our original paper was submitted for publication technological advances have permitted the introduction of greatly improved soybean milks which have much less tendency to cause gastrointestinal disturbances. In addition, two new medications have been introduced which are of great help in

the control of nonspecific diarrheas. These are an extract of the herb, *Erigeron canadensis*, colloquially known as "mule tail tea" or "Canada Fleabane," by Blue[7] and diiodohydroxyquinoline (Diodoquin—Searle) by Cohlan,[11] which have been exceedingly helpful in our experience in controlling loose bowel movements caused by soybean milk.

3. The alleged beneficial effects in the prophylaxis of allergic disease are due to the fact that because one child in the family had an allergic disease the environmental control instituted on that account—elimination of animal pets, feather pillows, wool blankets, reduction of house dust, and so on—is the important factor. This is a highly reasonable argument. However, the fact that the incidence of eczema in the series of breast-fed infants reported by Grulee and Sanford[36] and of all allergic diseases in the series reported by Kimball and Jorgensen[40] was so greatly reduced, with no thought of applying the principles of environmental control, is adequate negation of that argument.

4. The next objections to the use of soybean milk have been voiced principally by Fries.[19]

Perhaps the long-term feeding of soybean milk will ultimately result in some pathologic entity at present vague and unrecognized. The soybean has been used for centuries in China and other countries as a source of protein, owing to the inavailability and expense of meat and milk. Some orders of Buddhist monks have substituted soybean protein for animal protein all their lives without apparent deleterious effects. It would seem reasonable to suppose that if the soybean did have a deleterious effect on prolonged feeding, it would have been recognized by now. Our own controlled studies previously mentioned comparing infants fed soybean milk from birth and those fed cow's milk from birth[32] indicates that at the end of a year there were no differences in any measurable respects between the infants except that those started on soybean weighed somewhat more.

There are perhaps two principal reasons why the uninformed physician may fear to use a vegetable as the sole source of protein at this critical period of life. One is the general belief that vegetable protein is not as good biologically as an animal protein. This goes back to the work of Lui and associates,[44] who in 1931 stated that so far as hypoproteinemia in relation to edema is concerned, 2 gm. of vegetable protein are required to produce the same effect as 1 gm. of animal protein. They did not, however, take into consideration the soybean, which is the only member of the vegetable kingdom which has all the amino acids necessary for normal growth and development of the human infant. Block and Bolling[6] reviewed the evidence to the effect that the relative nutritional values of different proteins are based on their content of essential amino acids, i.e., those which cannot be synthesized in the animal body. The source of the amino acids, animal or vegetable, does not matter as long as they are supplied preformed in the diet.

That soybean feeding per se does not result in edema in the eczematous infant has been further discussed elsewhere.[28] Other publications[29] review the relative equality in digestibility of soybean protein as compared with cow's milk protein; its favorable protein efficiency ratio, the fact that the amino acid pattern of soybean is well suited for supplying the needs of the growing animal, and crucial experiments with newborn weanling rats indicate the superiority of soybean protein over cow's milk protein in supporting growth, reproduction and lactation in multiple generation feedings.

The only amino acid in which the soybean is somewhat deficient is methionine. Any objection to soybean protein on this basis is more theoretical than real, however, since this deficiency can be compensated by the additional ingestion of soybean protein (about 11 per cent of the minimal requirements for cow's milk protein) which these infants normally take in the course of satisfying their appetites.

Sternberg and Greenblatt[51] have reviewed the literature indicating the lack of evidence of harm caused by a diet most of whose protein is obtained from vegetable sources. In their series of infants fed soybean milk from birth no alterations in the serum proteins were found, and none had hypoproteinemia. Since, after the first three months of life, other foods are commonly added to the infant's diet, including animal proteins, these authors feel that soybean milk may be used in the newborn when indicated without fear of detrimental effects caused by diminished intake of animal protein.

5. Fries[18] further advised against the use of soybean milk because of the trypsin-inhibiting factor in the soybean and because the soybean is said to have goitrogenic properties. It is true that a trypsin inhibitor is present in large quantities in the soybean,[8, 41] but modern methods of preparing soybean milk completely inactivate this inhibitor. Furthermore, there are large amounts of trypsin inhibitor in bovine colostrum and even small quantities in human colostrum. The inhibitor in bovine colostrum is said to be 2.3 times as potent as the trypsin inhibitor of soybean. The significance of the trypsin-inhibiting factor in cow's and human colostrum is not positively known.[42] Hill and Stuart[39] introduced the first practical commercial preparation of soybean milk in 1929. The author and Fries* know of no difficulty with soybean milk, due to the presence of this inhibitor, reported since then.

6. Certain foods do have goitrogenic properties. This subject was reviewed by Greer[35] and by Fertman,[17] who stated that it is entirely possible that, when the dietary intake is limited almost entirely to these foods, the amount of antithyroid substance ingested may be sufficient to prevent thyroxin synthesis and thereby cause thyroid enlargement. Young rats fed exclusively on soybean will have large goiters as com-

* Personal communication.

pared with control rats, but this may be completely prevented by giving the rats a normal amount of iodine in their diet. Greer also stated that cooking of the vegetable before eating will probably prevent goitrogenesis. Whatever the facts are in experimental animals, in a long experience I have never seen any evidence of goiter in infants fed soybean milk as their sole source of protein for many weeks. Hill,* Stoesser* and Fries* also have never seen goiter associated with soybean ingestion.

Winship[55] has, however, reported that a number of childhood goiters have been examined which were thought to be produced by a diet rich in soybeans. In some cases a total thyroidectomy had been performed, and the entire gland showed a picture of juvenile hyperplasia. In most of the patients only one lobe was removed, and the contralateral lobe eventually returned to normal size without therapy and in some cases without alteration of the diet. He stated that no data have been presented to *prove* any goitrogenic or carcinogenic effect of soybeans.

This past year I have had personal reports, more or less incomplete, of three infants in whom it appeared that enlargement of the thyroid developed as a result of prolonged feeding of soybean milk. This is now the subject of intensive investigation.† Certainly well over a million babies have been fed soybean milk, in many instances for long periods of time, without the development of goiter, and the fact that only three presumptive cases have been reported suggests that either the goitrogenic substance in soybean is destroyed in the process of preparation of the soybean milk or that there is sufficient iodine in the preparation or accessory food substances fed the baby along with the soybean milk so that goitrogenesis will not result. Since only 3 possible cases of goiter due to soybean milk have appeared in almost 30 years, it would also be important to know the usual incidence of thyroid hyperplasia in the general infant population. If it should eventually be proved that the feeding of soybean milk will cause goitrogenesis, it would be a simple matter to add sufficient iodine to prevent this.‡

7. Fries[19] has also pointed out that feeding soybean milk to the newborn may sensitize the infant to related legumes (see also p. 876). In our experience of almost 30 years in the feeding of soybean milk to the newborn and to young infants and children, we have never observed this to happen, although admittedly it might happen and could easily be overlooked. We have, like Fries, seen an occasional positive skin reaction to soybean protein in an older child who had received soybean milk as an infant, but in no instance did this have clinical significance. Even if clinical sensitization to legumes did develop, it would be a

* Personal communications.

† This will be the subject of a report by Dr. J. J. VanWyk of the Department of Pediatrics of the University of North Carolina Medical School.

‡ This has already been done (personal communication from Dr. David W. Anderson, Director of Research, the Borden Company).

small price to pay for protection against allergic disease, since legumes are easily omitted from the diet.

8. Perhaps the least reasonable objection to the use of soybean milk as a substitute for cow's milk in the feeding of the newborn for the prophylaxis of allergic disease is that no explanation has been advanced as to why this procedure should prevent subsequent allergic disease, even though it is completely logical that the feeding of soybean milk will prevent allergy to cow's milk during the newborn period. This objection ignores the basic principle that, from the scientific standpoint, it is not necessary, however highly desirable, to explain a fact.

The most common allergic disease by far during the first six months of life is atopic dermatitis.[20] This disease, once established, may become highly resistant to all forms of treatment, and the allergens causing its persistence cannot be determined. Sulzberger[51a] suggested, and also reviewed the evidence to the effect, that this may be due to autosensitization brought about by damage to the skin by infection, by physical agents or by allergens producing and liberating skin antigen, which may then produce skin-specific antibodies which may cause reactions in the skin itself, thus perpetuating the cutaneous disorder. Possibly a similar mechanism is responsible for the persistence of other allergic diseases. If this hypothesis is correct as regards atopic dermatitis, its prophylaxis for this reason alone becomes a matter of paramount importance.

The high incidence of subsequent allergic disease in children who have suffered from atopic dermatitis (allergic eczema) is well documented. Ratner and associates[47] estimated 59 per cent, Vowles and associates,[52] 72 per cent, and the studies in my own practice,[21] an incidence of 80 per cent. This last figure is higher than the others, probably because recurrent upper respiratory tract disorder of allergic origin and perennial allergic rhinitis sufficiently severe to require thorough allergic study are included. Our early findings, previously referred to, that about *four* times as many potentially allergic infants fed cow's milk from birth develop eczema as compared with those started on soybean milk, and our later findings that about *four* times as many infants fed cow's milk from birth as those started on soybean milk later develop allergies, are not very likely mere coincidence. *It therefore seems reasonable that if atopic dermatitis can be prevented, subsequent allergic disease may be reduced.* A theory which may possibly explain this is as follows:

Just as insulin and related mechanisms are believed to prevent damage to the human organism by faulty carbohydrate metabolism, in the same way we doubtless have a mechanism which protects against damaging (allergic) reactions to proteins and other substances which may at times act as allergens. It seems reasonable to suppose that this latter protective mechanism is in some way related to the activities of the

hypothalamus-pituitary-adrenal axis. However, just as proteins are much more complex compounds than carbohydrates, so the mechanism for protection against these compounds is probably, though of course not necessarily, much more complex than the mechanism protecting against faulty carbohydrate metabolism. If we can relieve stress on this mechanism in early infancy by feeding a relatively nonallergenic food, such as soybean milk, instead of a food which has a high sensitization potential such as cow's milk, we may be able to avoid straining this mechanism. It might otherwise be so overworked by the early feeding of cow's milk in those predisposed by heredity to allergic disease that, because of this damaged mechanism, they will not be able to resist the development of other allergic diseases as age advances, and eczema will result.

The emphasis in pediatric practice in recent years has been on prophylaxis; therefore the responsibility for the prophylaxis of allergic diseases, most of which start in childhood, weighs heavily upon the pediatrician. The importance of this is indicated by the following statement from a recent publication by Peshkin:[45] "At least 10 per cent of the population of this country or 16,500,000 suffer from some form of allergy in need of treatments. Of the chronic diseases in this country allergy ranks third in prevalence with heart disease and mental illness taking the first two positions. There are 50,500,000 children up to 15 years of age, 5,000,000 of whom have allergy and at least 2,500,000 of whom have asthma and hay fever." Further emphasis is lent to the importance of the prophylaxis of asthma by the report of Dees[15] to the effect that asthma kills five times as many people (all ages included) as poliomyelitis. Her statistics were assembled before the general use of the Salk vaccine and before modern hormone therapy of asthma.

One can only conclude from the foregoing that the problem of the prophylaxis of allergic disease is of great importance to the pediatrician. Its sad neglect is indicated by the few discussions of this subject which have appeared in the literature. These observations suggest that pediatric teaching needs reorientation in the direction of more emphasis on allergy. Such reorientation rests in the hands of those responsible for our medical school curriculums.

SUMMARY AND CONCLUSIONS

1. Probably the best prophylaxis for allergic disease is breast feeding. It seems reasonable to suppose that the mother should be on a controlled diet to avoid foods of high sensitization potential during lactation, and perhaps during pregnancy.

2. If breast feeding is not practical, cow's milk, which has a high sensitization potential, should not be used. Soybean milk has proved to be an adequate substitute and should be given from birth or as a complementary or supplementary feeding for breast milk.

3. In our hands the incidence of subsequent allergic disease in potentially allergic children by the use of this procedure has been reduced from about 60 to about 15 per cent by the age of six years.

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INSECT ALLERGY

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Over 4000 years elapsed between the hieroglyphic report that King Menes of Egypt was stung to death by a wasp or hornet[4, 18] and the recognition of the anaphylactic nature of such reactions by Waterhouse[17] in 1914. In the past half century a number of such cases of insect anaphylaxis and many reports of inhalant and contact allergy to insects have been published, and yet these patients are still considered to be in the category of medical curiosities by many physicians. However, there is a growing awareness of the importance of insects as a major cause of respiratory allergy, stimulated by the recent reports of Osgood,[11] Feinberg et al.,[4, 5] Perlman[13] and others, and a similar recognition of the importance of the anaphylactic type of insect allergy, following the classic work of Benson and Semenov[1] in 1930 along with the more recent studies of Rockwell,[15] Loveless and Fackler,[8] Mueller[9, 10] and others.

For purposes of discussion, insect allergy can be divided into (1) inhalant and contact type, which is analogous to natural sensitivity acquired by atopic persons to pollens, molds, dust, and so on; and (2) stinging and biting type, which is analogous to artificial sensitivity produced by injection of an antigen through the intact skin into a person who may or may not be atopic.

INHALATION AND CONTACT INSECT ALLERGY

Insect distribution ranges from the poles to the equator, and as Perlman[13] has described it, "The entire earth is filled with a terrestrial and aquatic insect fauna that lives and multiples and dies to litter the surface and contaminate the air." Disintegrated substances from insects in the soil and vegetation, according to Feinberg,[5] constitute an anti-

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genic dust to which everybody is exposed, and he believes that a large proportion of the allergic population suffers from such allergy. Inhalation or contact by sensitive persons with microscopic bits of insects may cause asthma, allergic rhinitis, conjunctivitis or atopic dermatitis. The various orders, genera and species of insects (class Hexapoda) that may be responsible are myriad in number and, collectively as an antigenic dust or individually and in swarms, may produce allergic symptoms. Probably the commonest examples of the latter are sensitivity to the caddis fly or May fly found near the breeding places of these insects, along streams and other bodies of water, particularly in the Great Lakes area.[6, 11]

Patients with seasonal patterns that do not entirely correspond to pollens or molds, and particularly those that have failed to improve with specific pollen and mold treatment, should be suspected of insect allergy. Patients with seasonal symptoms who fail to react on testing to pollens and molds should be similarly suspected. However, these allergens are not necessarily confined to outdoors and seasons, since one must consider such indoor insects as carpet beetles, flies and moths in patients with perennial symptoms when diagnosis and treatment with usual environmental allergens have failed to provide relief for their allergic symptoms.

Because of the large number of different insects and difficulty in obtaining them, testing may be a problem, and most allergists have resorted to using either a limited number of the commoner species or to mixtures, both courses being predicated on the available evidence that there are common antigens and cross sensitivities at the classification levels of genus and order. Scratch tests are commonly done, but, in certain instances, a further check by the intracutaneous method may be indicated, although many falsely positive reactions may be obtained by the intracutaneous tests unless high dilutions of testing material are used.[5] Specific circulating antibody was demonstrated by passive transfer in all Feinberg's[4] patients who gave positive tests by the scratch method. This report also revealed the existence of cross reactivity and suggested the possibility that such reactions might represent a common contaminant such as the microbial content of the insects' gastrointestinal tract. It must also be remembered that many insects carry large numbers of bacteria on their legs and wings. The need for prompt processing and careful extraction, both for testing and treatment material, has been emphasized by Perlman[13] in order to avoid inert material with resulting failures in testing and treatment.

Treatment by conventional hyposensitization methods is recommended, and successful results have been reported.[5, 6, 11, 13] If specific sensitivity to an individual insect can be demonstrated, treatment with extracts of that insect, if available, should be given. If testing reveals

skin sensitivity to two or more insects that correlate with the clinical history, then the use of a mixed extract is preferable. Starting doses can be determined by titration of skin tests. Perennial treatment with maintenance of maximum tolerated doses every three to six weeks for periods similar to conventional pollen treatment is recommended. Although constitutional reactions may occur, they have not been alarming, and apparently the degree of sensitivity is not of the exquisite anaphylactoid type found with allergic reactions to insect stings.

ALLERGIC REACTIONS TO STINGING AND BITING INSECTS

Certainly, no human being escapes the possibility of this type of sensitization to insects, since the injection or deposition of foreign material by insects in the act of feeding is probably a universal experience. Reports of urticarial and anaphylactoid reactions to many biting and stinging insects are to be found in the literature. The most common and most important are the stings of mosquitoes, bees and wasps, the first because of their frequency, and the two latter because of their severity. Recent papers[2, 3] on the severity and frequency of reactions to stings of the imported fire ant indicate that the increase and rapid spread of this insect throughout the southern states may constitute a serious allergic hazard in that area.

Allergic reactions to the bites of such insects as mosquitoes, gnats, ticks, bedbugs, fleas, lice and flies are frequently induced by the injection of saliva which prevents clotting and facilitates the insects' feeding. These reactions are usually urticarial and may be followed by papular, vesicular or eczematous lesions accompanied by edema and erythema resembling cellulitis. According to Sherman and Kessler,[16] papular urticaria in children appears to be due in most cases to allergic reactions from bites of arthropods, chiefly bedbugs. In addition to the allergic skin lesions, bites of these various insects occasionally result in mild but unpleasant systemic symptoms of edema, malaise and nausea, but reports of severe anaphylactic reactions and death are not known to the author and, if they exist, must be extremely rare. However, these patients are uncomfortable and at times incapacitated to a degree which justifies attempts at desensitization when exposure to the insect cannot be eliminated.

The severe allergic reactions to insect stings, with few exceptions, are due to the order Hymenoptera, which includes the bees, wasps and ants. In all cases it is helpful to differentiate between toxic and allergic reactions; if time allows, this should be done when the reaction occurs, since treatment may differ in detail. Symptoms of toxicity may be edema without urticaria, headache, fever, drowsiness, weakness, involuntary muscle spasm and convulsions. Patients receiving 10 or more stings at

one time should always be suspected of having a toxic reaction, although individuals vary in their response to the toxicity of venom. In one instance[7] a small child with 477 wasp stings survived the enormous amount of venom that must have been injected, which can be calculated at a minimum of 15 to 20 cc. However, in any question involving the presence of anaphylactic shock, this condition is so serious that emergency measures to combat it should be undertaken without delay, regardless of toxic symptoms.

Our experience[10] and a recent study by Parrish[12] indicate that severe and fatal reactions to insect stings probably occur a great deal more commonly than is generally supposed and may account for some of the sudden deaths occurring in the insect seasons, attributed to heart failure, heat prostration and other causes.

In allergic reactions to insect stings, symptoms may vary from itching, urticaria, edema and malaise to respiratory difficulty, dysphagia, gastrointestinal disturbances, collapse, unconsciousness and death. Cyanosis, fall in blood pressure and incontinence are signs indicating a shock reaction. As a rule, the shorter the time interval from sting to onset of symptoms, the more severe the reaction will be. In our study of over 80 patients,[10] 75 per cent had a family or personal history of other allergy. Apparently, atopic persons are more likely to become sensitized, and our atopic patients had a higher percentage of the more severe reactions than did the nonatopics. *Epinephrine or its other rapid-acting derivatives, supported by antihistamines, are the drugs to be administered immediately for a sting reaction.* Steroids, by any route,[14] are too slow in their action to be of any benefit for a rapidly progressing anaphylactic reaction, although they may be used for later relief of residual urticaria and edema or to combat the stress of a prolonged state of shock.

Identification of the insect causing the sting reaction is unreliable, particularly in the case of children, since the chief interest of the patients, on being stung, is to separate themselves from the insect as rapidly as possible. Correlation of the circumstances at the time, with the nesting habits and the presence or absence of a stinger in the wound, may give presumptive evidence for identification; but in no case can this be certain unless the insect is captured. Since multiple cross sensitivities exist in most patients and there is no reliable way to determine the exact situation in a given patient, identification assumes less importance than was originally supposed.

These patients may have exquisite sensitivity. In two children[10] intracutaneous testing with extracts of 1:1,000,000 dilution resulted in immediate shock reactions. In most cases each sting is followed by an increase in sensitivity. For these reasons great caution must be exercised in both testing and treatment. A dilution of 1:100,000,000 is rec-

ommended as a starting point if intracutaneous testing is done to titrate skin sensitivity. The practical value of this testing is in the determination of a safe level to start treatment and the elimination of unnecessary inoculations if possible.

All patients with a systemic reaction to the sting of a bee, wasp, hornet or yellow jacket should be treated. Use of a mixed extract of all 4 insects is recommended, starting with 0.05 cc. of the dilution, which gives an initial positive intracutaneous test to any one or more of the 4 insects. Although skin sensitivity usually parallels clinical sensitivity, there are exceptions; and patients with very severe sting reactions have had no demonstrable skin sensitivity. In such cases one should start treatment cautiously at high dilution levels; but dosage increases can be greater than usual until one approaches 1:1000 dilution. If serial intracutaneous testing is not done, treatment should always be started at the 1:100,000,000 dilution level.

Depending upon the rapidity with which protection is desired, weekly or twice-weekly increments in dosage are given with each dilution until a maintenance dose of 0.2 to 0.3 cc. of 1:100 is reached or until local reaction larger than a silver dollar is encountered twice with the same dose, after having dropped back and approached that dose a second time. In patients with little or no skin sensitivity the dose should be increased to 0.1 cc. of 1:10 dilution if tolerated without local or systemic reactions. The maintenance dose should then be given in all patients every four weeks in the insect seasons and every six weeks through the winter for a period of three years. Patients on treatment should carry with them a 15-mg. sublingual tablet of isoproterenol, and if stung before maintenance dosage is reached, they should take the tablet immediately and seek medical care. If stung after they are on maintenance dosage, they should not take the medication unless systemic symptoms appear. Once they have been stung without reaction, they may discard the medication.

Experience to date in the treatment of 76 patients[10] indicates that a high degree of protection is afforded by the treatment. With one exception, 30 of these patients who have been stung while on a maintenance dose of 0.15 cc. or greater of a 1:100 dilution of the mixed insect extract, or who have been stung after completing 3 years of treatment, have had no resulting systemic symptoms.

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